



US009085584B2

(12) **United States Patent**
Giovannini et al.

(10) **Patent No.:** **US 9,085,584 B2**
(45) **Date of Patent:** **Jul. 21, 2015**

(54) **SUBSTITUTED
PYRIDO[3,2-E][1,2,4]-TRIAZOLO[4,3-A]
PYRAZINES FOR THE TREATMENT OF
CENTRAL NERVOUS SYSTEM DISORDERS**

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(71) Applicants: **Riccardo Giovannini**, Verona (IT);
Barbara Bertani, Castiglione delle
Stiviere (IT); **Sara Frattini**, Castelleone
(IT); **Giustino Di Antonio**, Sant'Egidio
alla Vibrata (IT); **Hans-Joachim
Lankau**, Weinböhla (DE); **Hans Stange**,
Riesa (DE); **Christian Grunwald**,
Dresden (DE); **Norbert Höfgen**,
Ottendorf-Okrilla (DE); **Barbara
Langen**, Radebeul (DE); **Ute Egerland**,
Radebeul (DE)

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(72) Inventors: **Riccardo Giovannini**, Verona (IT);
Barbara Bertani, Castiglione delle
Stiviere (IT); **Sara Frattini**, Castelleone
(IT); **Giustino Di Antonio**, Sant'Egidio
alla Vibrata (IT); **Hans-Joachim
Lankau**, Weinböhla (DE); **Hans Stange**,
Riesa (DE); **Christian Grunwald**,
Dresden (DE); **Norbert Höfgen**,
Ottendorf-Okrilla (DE); **Barbara
Langen**, Radebeul (DE); **Ute Egerland**,
Radebeul (DE)

(73) Assignee: **Boehringer Ingelheim International
GmbH**, Ingelheim am Rhein (DE)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/951,531**

(22) Filed: **Jul. 26, 2013**

(65) **Prior Publication Data**

US 2014/0045857 A1 Feb. 13, 2014

(30) **Foreign Application Priority Data**

Jul. 31, 2012 (EP) 12178713

(51) **Int. Cl.**

A61K 31/4985 (2006.01)
C07D 487/14 (2006.01)
C07D 471/14 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 487/14** (2013.01); **C07D 471/14**
(2013.01)

(58) **Field of Classification Search**

CPC **A61K 31/4985**; **C07D 487/14**
USPC 514/250; 544/346; 546/268.1; 549/356,
549/429, 510

See application file for complete search history.

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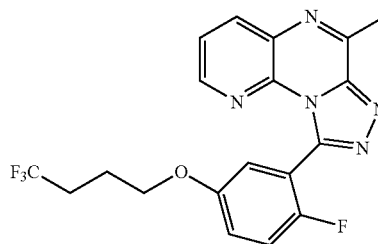
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Primary Examiner — Douglas M Willis

(74) *Attorney, Agent, or Firm* — Michael P. Morris; Alan R.
Stempel

(57) **ABSTRACT**

The compounds are of the class of pyrido[3,2-e][1,2,4]-tia-
zolo[4,3-a]pyrazines, useful in the treatment of central ner-
vous system disorders. A species illustrative of members of
the class is the following:



34 Claims, No Drawings

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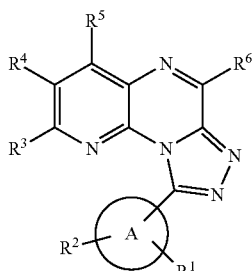
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**SUBSTITUTED
PYRIDO[3,2-E][1,2,4]-TRIAZOLO[4,3-A]
PYRAZINES FOR THE TREATMENT OF
CENTRAL NERVOUS SYSTEM DISORDERS**

FIELD OF THE INVENTION

The invention relates to 4-methyl-2,3,5,9b-pentaaza-cyclopenta[a]naphthalene derivatives of general formula (I) which are inhibitors of phosphodiesterase 2 and/or 10, useful in treating central nervous system diseases and other diseases. In addition, the invention relates to processes for preparing pharmaceutical compositions as well as processes for manufacture the compounds according to the invention.



BACKGROUND OF THE INVENTION

Cognitive dysfunction plays a role in a number of central nervous system disorders, including neurological disorders, such as Alzheimer's disease (AD), Parkinson disease and dementia, but also psychiatric disorders, such as schizophrenia, depression and bipolar disorders. As world population grows older the number of patients with dementia and AD is growing. Therefore, most people are familiar with the cognitive deficits related to these neurological diseases (Massoud and Gauthier, 2010).

However, also in psychiatric disorders cognitive impairment adversely affect the progress and the treatment outcome of the disease. A most prominent example is schizophrenia. Schizophrenia has a heterogeneous symptomatic picture (American Psychiatric Association, 1994) that may be divided into three distinct disease domains: positive symptoms (psychotic episodes of hallucinations, delusions and agitation), negative symptoms (social withdrawal, anhedonia, flattened affect) and cognitive deficits (deficits in executive function, verbal learning and memory, verbal fluency) (Thompson and Meltzer, 1993).

Whereas positive symptoms are essentially alleviated by dopamine D2 receptor antagonist and second generation antipsychotics negative symptoms and cognitive deficits are still hardly affected by current treatments. Therefore, research on cognitive deficits in schizophrenia has been intensified over the past years. A worldwide network initiative, called MATRICS, has been founded to characterise the cognitive deficits more deeply and to find novel therapies (Young et al., 2009).

However, cognitive impairment is also seen in patients with depression, bipolar disorders (Sachs et al., 2007; Pavuluri et al., 2009) and in many patients with disorders usually first diagnosed in infancy, childhood and adolescence, such as attention deficit/hyperactivity disorder (ADHD) (Jucaite et al., 2005; Turner et al., 2003).

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Depression is a severe mental disorder which extremely impairs daily life. Its prevalence is about 10% of the world population with an incidence of 2% according to WHO. Women are more affected than men and elder people more than younger people. The disorder mostly implies a life-long treatment due to the progression of the disease and permanent total disability.

The most prominent symptoms of the disease are anhedonia, feeling of hopelessness, decreased self esteem, loss of appetite and sleep disturbances. Suicide ideation is also a common symptom of depression and about 10% of depressed patients (Holma et al., 2010) attempt suicide. Depression is often combined with anxiety disorders. Interestingly, it is less known that depression is also regularly associated with various cognitive impairments (Gualtieri et al., 2006; Mandelli et al., 2006). Here, deficits of attentional and executive functions are mostly reported (Paelecke-Habermann et al., 2005). Cognitive deficits are even discussed to be involved in the development of the disease (Beck depression model, Beck, 2008). More recent studies indicate that the severity of the cognitive deficits may predict non-response to certain antidepressant treatment (Dunkin et al., 2000; Gorlyn et al., 2008).

Up to now, current antidepressant therapy seems not to be sufficient regarding cognitive deficits. Elder antidepressants are reported to impair memory in animal models of learning and memory probably due to their anticholinergic component (Kumar and Kulkarni, 1996). In contrast, SSRIs, in particular fluoxetine, are described to impair hippocampal-independent but not hippocampal dependent learning in different rodent models (Valluzi and Chan, 2007). At least, in clinic current therapy it is not possible to fully reverse cognitive deficits. Thus, in depressive patients who had been successfully treated cognitive performance could be improved but not normalised (Gualtieri et al., 2006). Therefore, an antidepressant with higher efficacy on cognitive impairment may improve disease outcome.

Bipolar disorders are characterized by complex symptomatology, including severe symptoms of mood disorders but also manic episodes and cognitive deficits. The Diagnostic and Statistical Manual, 4th edition and International Classification of Mental Disorder recommend subgroups of bipolar disorder based on whether depressive or manic [psychotic] symptoms and episodes are dominating and on the frequency of the episodes (Gaiwani, 2009). Pharmacological agents commonly used in the management of bipolar disorder include lithium; anticonvulsants, such as valproate, carbamazepine and lamotrigine; and recent years have witnessed increasing use of atypical antipsychotics (Altamura et al., 2011). As a problem of current therapy the development of tolerance against anticonvulsant treatment and 30% of treatment refractory cases are described (Post and Weiss, 2010; Gaiwani, 2009).

Attention deficit hyperactivity disorder (ADHD) is a central nervous system disorder that is mainly defined by its clinical signs. ADHD shows a heterogeneous symptom pattern in humans. The most important indicators are attention deficits, impulsivity and a hyperactivity that is primarily seen in boys. The disease starts at an early age and symptoms are most intense during childhood. After puberty the signs of the disease are more masked and focus on cognitive dysfunction (Jucaite et al. 2005; Turner et al. 2003). Although modern research broadened the understanding of the pathomechanism the exact etiology of the disease remains unclear.

Interestingly, the symptoms seen in ADHD are not due to a hyperactivity but a hypoactivity of the so called executive loop of the striatum (Winstanley et al., 2006; Pliszka, 2005). The executive loop is responsible for the regulation of cog-

nitive processes such as planning, working memory and attention (Benke et al., 2003; Easton et al., 2007). A dysfunction of the prefrontal cortex or other pathways within the loop induces impulsivity and a loss of the ability to filter stimuli that come from the outside. The latter causes the symptoms of sustained attention and hyperactivity (Roberts and Wallis, 2000; Gonzales et al., 2000). The dopaminergic neurotransmitter system plays a central role in regulating the activity of the executive loop (Jucaite et al., 2005). This conclusion is also supported by the current treatment for ADHD that aims for an activation of the dopaminergic neurotransmitter system (Jucaite et al., 2005).

Phosphodiesterases (PDE) are expressed in nearly all mammalian cells. To date eleven families of phosphodiesterases have been identified in mammals (Essayan, 2001). It is well established that PDEs are critically involved in cell signalling. Specifically, PDEs are known to inactivate the cyclic nucleotides cAMP and/or cGMP (Soderling and Beavo, 2000). The cyclic nucleotides cAMP and cGMP are synthesised by the adenylyl and guanylyl cyclases and are second messengers that control many key cellular functions. The synthesis of cAMP and cGMP is regulated by different G-protein-coupled receptor types including dopamine D1 and D2 receptors (Mutschler, 2001).

The phosphodiesterases of the different families vary in their substrate selectivity. Thus, some families only hydrolyse cAMP others only cGMP. Some phosphodiesterases, such as phosphodiesterase 2 and 10, inactivate both cAMP and cGMP (Menniti et al., 2006).

Furthermore, there is a difference in the distribution of the different phosphodiesterases within the organism and additionally, within any particular tissue or organ. For instance, the distribution pattern of the phosphodiesterases within the brain is quite specific (Menniti et al., 2006).

Finally, phosphodiesterase families have different regulatory properties and intracellular location; some are bound to cell membranes and some are dissociated in the cytoplasm, additionally, a division into various intracellular compartments has been reported (Conti and Jin, 1999).

These differences in the function and location of the different PDE enzyme families suggest that the individual phosphodiesterases are selectively involved in regulating many different physiological processes. Accordingly, selective phosphodiesterase inhibitors may with fine specificity regulate different physiological and pathophysiological processes.

PDE2 and PDE10 hydrolyse both, cGMP and cAMP (Menniti et al., 2006; Soderling et al., 1999; Kotera et al., 1999).

They are both abundantly expressed in the brain indicating their relevance in CNS function (Bolger et al., 1994; Menniti et al., 2001).

PDE2 mRNA is mainly distributed in olfactory bulb, olfactory tubercle, cortex, amygdala, striatum, and hippocampus (Lakics et al., 2005; van Staveren et al., 2003). PDE10 (PDE10A) is primarily expressed in the nucleus accumbens and the caudate putamen. Areas with moderate expression are the thalamus, hippocampus, frontal cortex and olfactory tubercle (Menniti et al., 2001).

Although there are certainly fine differences in the function and expression patterns of PDE2 and 10, the expression of PDE2 in the hippocampus, the cortex and in the striatum and the expression of PDE10 in striatum, hippocampus and frontal cortex indicate an involvement in the mechanism of learning and memory/cognition. This is further supported by the fact that increased levels of both cGMP and cAMP are involved in the process of short and long term potentiation

(LTP) forming (Blokland et al., 2006; Prickaerts et al., 2002). LTP is regarded as the electrophysiological basis of long term memory (Baddeley, 2003). Boess et al. (2004) showed that PDE2 inhibitors amplify the generation of LTP. Additionally, it is reported that the selective PDE2 inhibitor BAY60-7550 enhances learning and memory in rats and mice in different animal models (Boess et al., 2004; Rutten et al., 2006). Similar pro-cognitive effects are described for selective PDE10 inhibitors, such as papaverine and MP-10. Rodefer et al. (2005) have found that papaverine reverses attentional set-shifting deficits induced by subchronic administration of phencyclidine, an NMDA antagonist, in rats. Grauer et al. (2009) could show a positive effect of papaverine and MP-10 on cognitive deficits in the novel object recognition and in prepulse inhibition of acoustic startle response in rats. These data support the procognitive effect of PDE2 and/or 10 and a synergistic effect of PDE2 and 10 on cognition.

Furthermore, the expression of PDE2 in the nucleus accumbens (part of the striatum), the olfactory bulb, the olfactory tubercle and the amygdala and the expression of PDE10 in the nucleus accumbens, the olfactory tubercle and the thalamus supports additional involvement of PDE2 and 10 in the pathophysiology of anxiety and depression (Modell et al., 1990). This is supported by in vivo studies. The selective PDE2 inhibitors BAY60-7550 and ND-7001 are described to be effective in animal models of anxiety and stress-induced behavior (Masood et al., 2008, 2009).

In addition to the pro-cognitive and antidepressant potential of PDE10 inhibition there is evidence for an additional antipsychotic potential of PDE10 inhibitors. In the striatum PDE10 is predominately found postsynaptic in the medium spiny neurons (Xie et al., 2006). By this location, PDE10 may have an important influence on the signal cascade induced by dopaminergic and glutamatergic input on the striatum, two neurotransmitter systems playing a predominate role in the pathomechanism of psychosis. Focusing on the dopaminergic input on the medium spiny neurons, PDE10A inhibitors by up-regulating cAMP and cGMP levels act as D1 agonists and D2 antagonists because the activation of Gs-protein coupled dopamine D1 receptor increases intracellular cAMP, whereas the activation of the Gi-protein coupled dopamine D2 receptor decreases intracellular cAMP levels through inhibition of adenylyl cyclase activity (Mutschler et al., 2001). Accordingly, PDE10 inhibitors are reported to be active in several animal models of schizophrenia (Schmidt et al., 2008; Siuciak et al., 2006; Grauer et al., 2009).

PDE10 inhibitors have been disclosed recently in J. Med. Chem, 2011, 54, 7621-7638.

For drugs with an intended action in the central nervous system (CNS), it is assumed that unbound drug in interstitial spaces in the brain is in direct contact or in equilibrium with the site of action (de Lange and Danhof, 2002).

It is commonly accepted that unbound or free drug is the species available for interaction with drug targets within the body, and this is referred to as the free drug hypothesis.

Because cerebrospinal fluid (CSF) is in direct contact with the brain tissue, it is assumed to readily equilibrate with brain interstitial fluid concentration (Meineke et al., 2002; Shen et al., 2004) so that CSF concentration is used as a common surrogate measure for drug unbound concentration in clinical pharmacology studies (Bonati et al., 1982; Cherubin et al., 1989; Garver, 1989; Reiter and Doron, 1996; Ostermann et al., 2004). Accordingly, for compounds with an intended action in the central nervous system it is important that they reach a high CSF concentration and a high CSF to plasma ratio in order to have high pharmacological activity in the CNS.

Inhibition of the hERG channel by xenobiotics and subsequent delayed cardiac repolarization is associated with an increased risk for a specific polymorphic ventricular tachyarrhythmia, torsade de pointes, as established by Sanguinetti et al. (1995, *Cell*, April 21, 81(2):299-307) and a large body of subsequent evidence. As such, low hERG channel inhibition, such as that shown by the compounds of the present invention, is highly desirable for therapeutics.

Several families of PDE2 inhibitors are known. Imidazotriazinones are claimed in WO 2002/068423 for the treatment of e.g. memory deficiency, cognitive disorders, dementia and Alzheimer's disease. Oxindoles are described in WO 2005/041957 for the treatment of dementia. Further inhibitors of PDE2 are known from WO 2007/121319 for the treatment of anxiety and depression, from WO 2013/034761, WO 2012/104293 and WO 2013/000924 for the treatment of neurological and psychiatric disorders, from WO 2006/072615, WO 2006/072612, WO 2006/024640 and WO 2005/113517 for the treatment of arthritis, cancer, edema and septic shock, from WO 2005/063723 for the treatment of renal and liver failure, liver dysfunction, restless leg syndrome, rheumatic disorders, arthritis, rhinitis, asthma and obesity, from WO 2005/041957 for the treatment of cancer and thrombotic disorders, from WO 2006/102728 for the treatment of angina pectoris and hypertension from WO 2008/043461 for the treatment of cardiovascular disorders, erectile dysfunction, inflammation and renal failure and from WO 2005/061497 for the treatment of e.g. dementia, memory disorders, cancer and osteoporosis.

Finally, benzodiazepines are described in WO 2005/063723 for the general treatment of CNS diseases including anxiety, depression, ADHD, neurodegeneration, Alzheimer's disease and psychosis.

AIM OF THE INVENTION

It has now been found that compounds of the present invention according to general formula I are effective inhibitors of phosphodiesterase 2 and/or 10. Besides the inhibition property toward phosphodiesterase 2 and/or 10 enzymes, the compounds of the present invention provide further advantageous pharmacokinetic properties. For example the compounds of the present invention show high concentration in cerebrospinal fluid (CSF) and have a high CSF to plasma ratio, which translates in lower efficacious doses of the compounds for disease treatment and as a consequence in further potential advantages such as minimization of side effects. Furthermore, compounds of the present inventions show good metabolic stability and low potential of formation of biologically active metabolite and low hERG potassium channel inhibition.

Accordingly, one aspect of the invention refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and salts thereof as inhibitors of phosphodiesterase 2 and/or 10.

Another aspect of the invention refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 and reaching high concentrations in cerebrospinal fluid (CSF) and/or having high CSF to plasma ratio.

Another aspect of the invention refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts

thereof as inhibitors of phosphodiesterase 2 and/or 10 and showing good metabolic stability.

Another aspect of the invention refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 with low hERG channel inhibition.

Another aspect of the invention refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 with low potential of forming biologically active metabolite.

In a further aspect this invention relates to pharmaceutical compositions, containing at least one compound according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof optionally together with one or more inert carriers and/or diluents.

A further aspect of the present invention relates to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof or pharmaceutical compositions comprising compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof for the use in the prevention and/or treatment of disorders associated with PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction.

Another aspect of the invention relates to processes of manufacture of the compounds of the present invention.

A further aspect of the present invention relates to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof or pharmaceutical compositions comprising compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof for the use in the prevention and/or treatment of diseases or conditions which can be influenced by inhibition of PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction, such as (1) disorders comprising the symptom of cognitive deficiency; (2) organic, including symptomatic, mental disorders, dementia; (3) mental retardation; (4) mood affective disorders; (5) neurotic, stress-related and somatoform disorders including anxiety disorders; (6) behavioural and emotional disorders with onset usually occurring in childhood and adolescence, attention deficit hyperactivity syndrome (ADHD) including Autism spectrum disorders; (7) disorders of psychological development, developmental disorders of scholastic skills; (8) schizophrenia and other psychotic disorders; (9) disorders of adult personality and behaviour; (10) mental and behavioural disorders due to psychoactive substance use; (11) extrapyramidal and movement disorders; (12) episodic and paroxysmal disorders, epilepsy; (13) Systemic atrophies primarily affecting the central nervous system, ataxia; (14) Behavioural syndromes associated with physiological disturbances and physical factors; (15) sexual dysfunction comprising excessive sexual drive; (16) factitious disorders.

In addition, the compounds of the present invention can be used for the treatment, amelioration and/or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

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In addition, the compounds of the present invention can be used for the treatment amelioration and/or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

In addition, the compounds of the present invention can be used for the treatment of Alzheimer's disease.

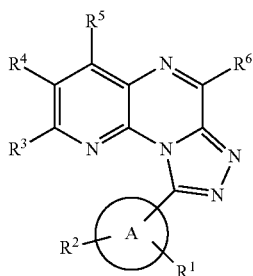
In addition compounds of the present invention can be used for the treatment of pain disorders, including but not limited to inflammatory, neuropathic and osteoarthritic pain.

In addition, the compounds of the present invention can be used for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

Other aims of the present invention will become apparent to the skilled man directly from the foregoing and following remarks.

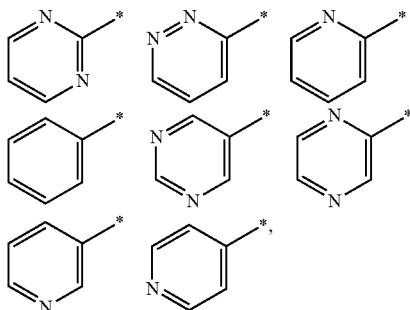
DETAILED DESCRIPTION

In a first aspect the present invention relates to compounds of general formula I



wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl and pyrazinyl groups are substituted with R¹ and R²;

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R¹ is selected from the group R^{1a} consisting of

H, halogen, NC—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— with n=0, 1, 2, 3 or 4, wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO— and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R² is selected from the group R^{2a} consisting of

H, HO—, halogen, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— with n=0, 1, 2, 3 or 4, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0, 1 or 2 and o=0, 1 or 2, wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O—groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R³ is selected from the group R^{3a} consisting of

H, halogen, NC—, C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-, wherein the above mentioned C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC—, HO—, C₁₋₃-alkyl- and C₁₋₃-alkyl-O—;

R⁴, R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC—, HO—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O—, wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O—groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O—;

R⁶ is selected from the group R^{6a} consisting of

H, NC—, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O— wherein above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of

H, carbocyclyl, heterocyclyl and heteroaryl, wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of HO—, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-O— and halogen;

R⁸ is selected from the group R^{8a} consisting of

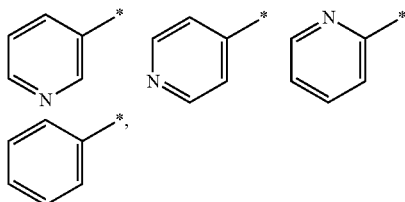
C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl, wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-;

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the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

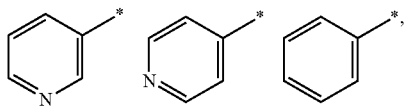
Unless otherwise stated, the groups, residues, and substituents, particularly R^1 , R^2 , R^3 , $R^{4/5}$, R^6 , R^7 , R^8 and A are defined as above and hereinafter. If residues, substituents, or groups occur several times in a compound they may have the same or different meanings. Some preferred meanings of groups and substituents of the compounds according to the invention will be given hereinafter.

In a further embodiment of the present invention A is selected from the group A^b consisting of



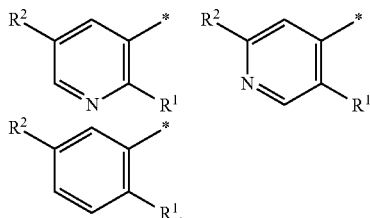
wherein above mentioned phenyl- and pyridinyl- groups are substituted with R^1 and R^2 .

In a further embodiment of the present invention A is selected from the group A^c consisting of

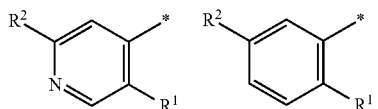


wherein above mentioned phenyl- and pyridinyl- groups are substituted with R^1 and R^2 .

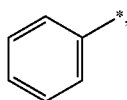
In a further embodiment of the present invention A is selected from the group A^d consisting of



In a further embodiment of the present invention A is selected from the group A^e consisting of



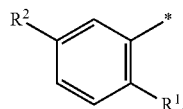
In a further embodiment of the present invention A is selected from the group A^f consisting of



wherein above mentioned phenyl-group is substituted with R^1 and R^2 .

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In a further embodiment of the present invention A is selected from the group A^9 consisting of



In a further embodiment of the present invention R^1 is selected from the group R^{1b} consisting of

H, halogen, C_{1-6} -alkyl- and C_{3-6} -cycloalkyl

wherein above mentioned C_{1-6} -alkyl- and C_{3-6} -cycloalkyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO— and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-.

In a further embodiment of the present invention

R^1 is selected from the group R^{1c} consisting of H, H_3C —, F_3C —, F_2HC —, FH_2C —, fluorine, chlorine and bromine.

In a further embodiment of the present invention

R^1 is selected from the group R^{1c1} consisting of

H_3C —, fluorine and chlorine.

In a further embodiment of the present invention

R^1 is selected from the group R^{1d} consisting of H, fluorine and chlorine.

In a further embodiment of the present invention

R^2 is selected from the group R^{2a1} consisting of

HO—, C_{1-6} -alkyl-, C_{1-6} -alkyl-O—, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl-, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, $R^8-(CH_2)_n-O$ — with $n=0, 1, 2, 3$ or 4 , and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o-O$ — with $m=0, 1$ or 2 and $o=0, 1$ or 2

wherein above mentioned C_{1-6} -alkyl- and C_{1-6} -alkyl-O-groups are substituted with 1 to 5 substituents independently selected from the group consisting of HO—, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-O—,

and

wherein above mentioned C_{1-6} -alkyl- and C_{1-6} -alkyl-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-,

and

wherein above mentioned C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl-, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, $R^8-(CH_2)_n-O$ — and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o-O$ -groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-.

In a further embodiment of the present invention

R^2 is selected from the group R^{2b} consisting of

H, HO—, C_{1-4} -alkyl-, C_{1-4} -alkyl-O—, C_{3-6} -cycloalkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, $R^8-(CH_2)_n-O$ — with $n=0, 1, 2$ or 3 and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o-O$ — with $m=0$ or 1 and $o=0$ or 1

wherein above mentioned C_{1-4} -alkyl-, C_{1-4} -alkyl-O—, C_{3-6} -cycloalkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, $R^8-(CH_2)_n-O$ — and $R^8-(CH_2)_m-(CH)(CH_3)-(CH_2)_o-O$ -groups may optionally be sub-

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stituted with 1 to 3 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention R² is selected from the group R^{2b1} consisting of

HO—, C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— with n=0, 1, 2 or 3 and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0 or 1 and o=0 or 1

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups are substituted with 1 to 3 substituents independently selected from the group consisting of HO— and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—,

and

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

wherein above mentioned C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention R² is selected from the group R^{2c} consisting of

H, HO—, C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, C₃₋₆-cycloalkyl, heterocyclyl, R⁸—(CH₂)_n—O— with n=0, 1, 2, or 3, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0 or 1 and o=0 or 1

wherein above mentioned C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, C₃₋₆-cycloalkyl, heterocyclyl, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention R² is selected from the group R^{2c1} consisting of

HO—, C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, R⁸—(CH₂)_n—O— with n=0, 1, 2, or 3, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0 or 1 and o=0 or 1

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups are substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of HO—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—,

and

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

wherein above mentioned C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected

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from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

R² is selected from the group R^{2d} consisting of

H, HO—, C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, a saturated 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸—(CH₂)_n—O— with n=0, 1 or 2, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0 or 1 and o=0 or 1

wherein above mentioned C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, saturated 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

In a further embodiment of the present invention

R² is selected from the group R^{2d1} consisting of

HO—, C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, a saturated 5 or 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸—(CH₂)_n—O— with n=0, 1 or 2, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0 or 1 and o=0 or 1

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups are substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of HO—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—,

and

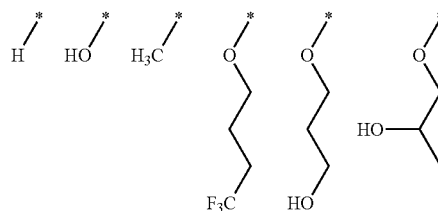
wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

wherein above mentioned C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, saturated 5 or 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-.

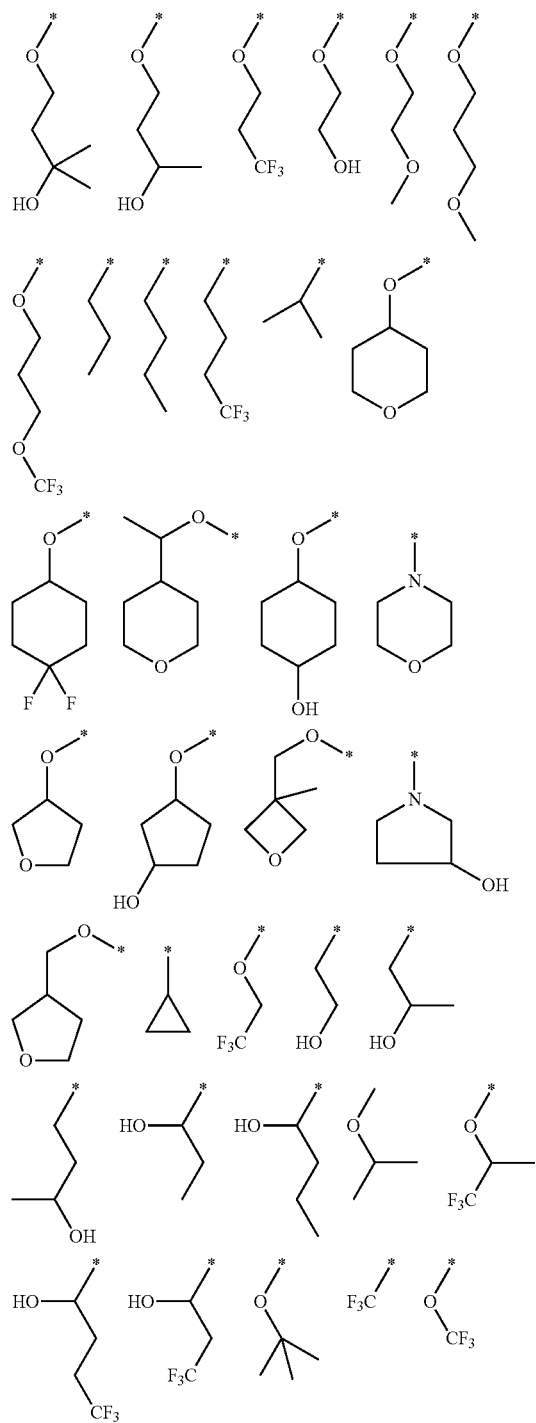
In a further embodiment of the present invention

R² is selected from the group R^{2e} consisting of

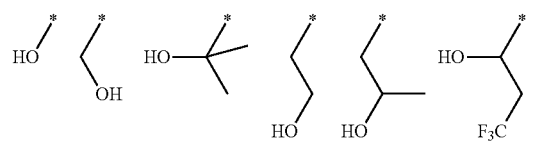


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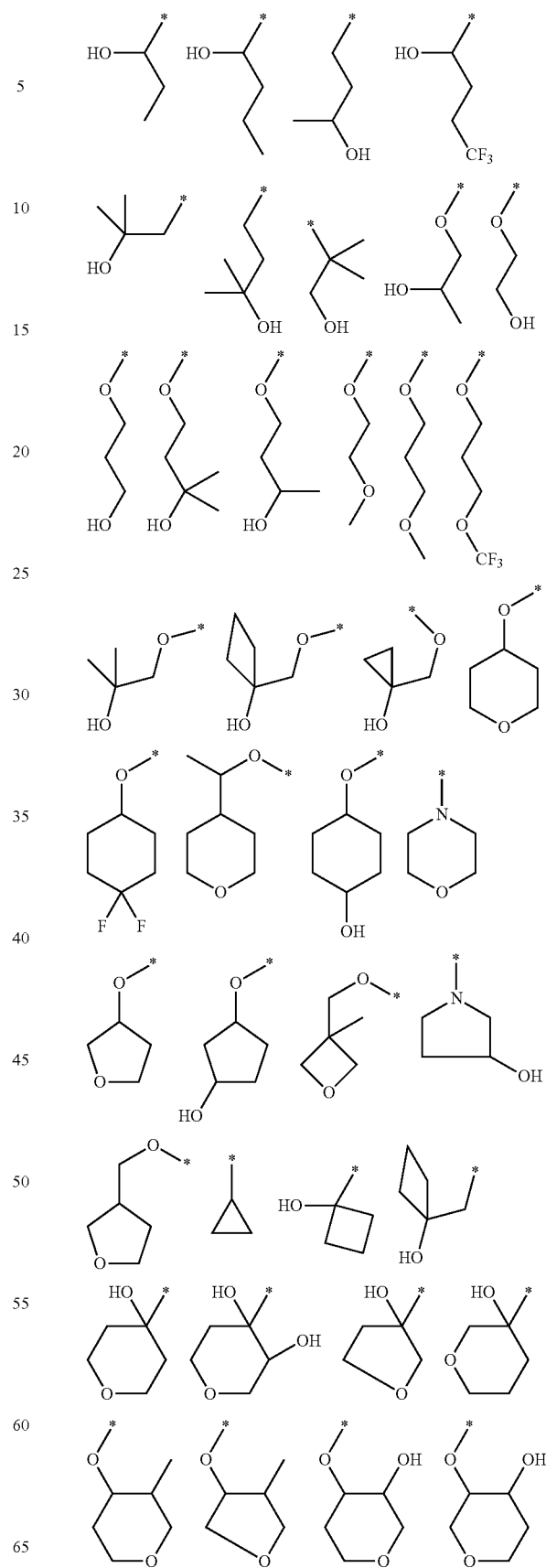
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In a further embodiment of the present invention
 R^2 is selected from the group R^{2e1} consisting of

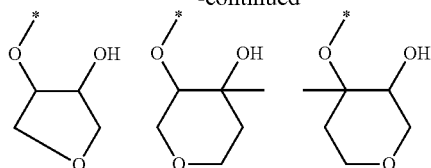
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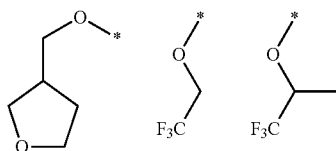
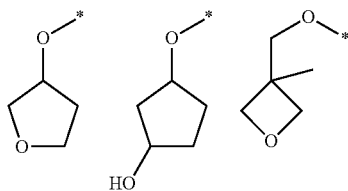
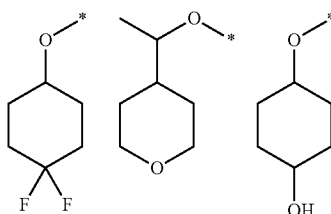
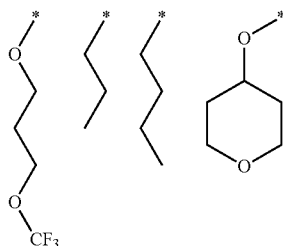
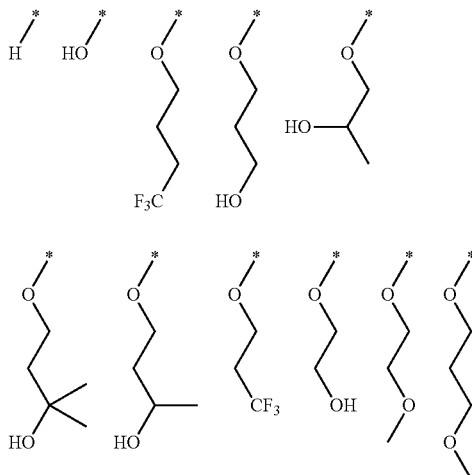


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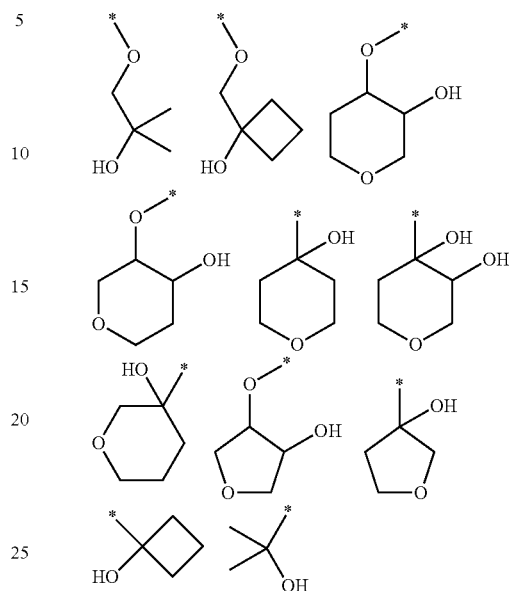


In a further embodiment of the present invention R^2 is selected from the group R^{2f} consisting of



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In a further embodiment of the present invention R^2 is selected from the group R^{2a} consisting of



In a further embodiment of the present invention
30 R^3 is selected from the group R^{3a1} consisting of

C₃₋₆-cycloalkyl-,
wherein the above mentioned C₃₋₆-cycloalkyl-group
may optionally be substituted with 1 to 9 substituents
independently selected from the group consisting of
halogen, NC—, HO—, C₁₋₃-alkyl- and C₁₋₃-alkyl-
O—.

In a further embodiment of the present invention
R³ is selected from the group R^{3b} consisting of
40 H, C₁₋₃-alkyl-, cyclobutyl- and cyclopropyl-,
wherein the above mentioned C₁₋₃-alkyl-, cyclobutyl-
and cyclopropyl-groups may optionally be substi-
tuted with 1 to 7 substituents independently selected
from the group consisting of halogen, C₁₋₃-alkyl-
45 O—, NC— and HO—.

In a further embodiment of the present invention R³ is selected from the group R^{3c} consisting of H, and H₃C— and cyclopropyl-,
50 wherein the above mentioned H₃C— and cyclopropyl- groups may optionally be substituted with 1 to 3 fluorine atoms.

In a further embodiment of the present invention
 R^3 is selected from the group R^{3d} consisting of
 55 H and H_3C- ,
 wherein the above mentioned H_3C -group may option-
 ally be substituted with 1 to 3 fluorine atoms.

In a further embodiment of the present invention
60 R^3 is selected from the group R^{3e} consisting of
H.

In a further embodiment of the present invention R³ is selected from the group R^{3f} consisting of

65 H₃C—, wherein the above mentioned H₃C-group may optionally be substituted with 1 to 3 fluorine atoms.

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In a further embodiment of the present invention R^3 is selected from the group R^{3g} consisting of cyclopropyl-,

wherein the above mentioned cyclopropyl-group may optionally be substituted with 1 to 7 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl-O—, NC— and HO—.

In a further embodiment of the present invention R^4 , R^5 are selected independently of each other from the group R^{4b}/R^{5b} consisting of

H, halogen, HO—, H_3C —, F_3C —, H_3C —O—, F_2HC —O—, FH_2C —O—, F_3C —O—, C_{1-4} -alkyl-O—, R^7-CH_2-O — and $R^7-(CH_2)_2-O$ —,

wherein above mentioned C_{1-4} -alkyl-O—, R^7-CH_2-O — and $R^7-(CH_2)_2-O$ — groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms substituted C_{1-2} -alkyl-, and optionally with 1 to 5 halogen atoms substituted C_{1-2} -alkyl-O—.

In a further embodiment of the present invention R^4 , R^5 are selected independently of each other from the group R^{4c}/R^{5c} consisting of

H, fluorine, chlorine, bromine, HO—, H_3C —, F_3C —, H_3C —O—, F_3C —O— and R^7-CH_2-O —.

In a further embodiment of the present invention R^4 , R^5 are selected from the group R^{4d}/R^{5d} consisting of H—.

In a further embodiment of the present invention R^6 is selected from the group R^{6b} consisting of

H, C_{1-4} -alkyl- and cyclopropyl-, wherein above mentioned C_{1-4} -alkyl-group may optionally be substituted with 1-9 fluorine and/or chlorine atoms.

In a further embodiment of the present invention R^6 is selected from the group R^{6c} consisting of H and C_{1-2} -alkyl-,

wherein above mentioned C_{1-2} -alkyl- group may optionally be substituted with 1-5 fluorine and/or chlorine atoms.

In a further embodiment of the present invention R^6 is selected from the group R^{6d} consisting of H, H_3C —, FH_2C —, F_2HC — and F_3C —.

In a further embodiment of the present invention R^6 is selected from the group R^{6e} consisting of H_3C —, FH_2C —, F_2HC — and F_3C —.

In a further embodiment of the present invention R^6 is selected from the group R^{6f} consisting of H_3C —.

In a further embodiment of the present invention R^7 is selected from the group R^{7b} consisting of

H, phenyl, heteroaryl, cycloalkyl and heterocyclyl wherein above mentioned phenyl, heteroaryl, cycloalkyl and heterocyclyl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, and optionally with 1 to 3 halogen atoms substituted C_{1-3} -alkyl-O—.

In a further embodiment of the present invention R^7 is selected from the group R^{7c} consisting of

H and phenyl, wherein above mentioned phenyl group may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen and optionally with 1 to 3 halogen atoms substituted C_{1-3} -alkyl-O—.

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In a further embodiment of the present invention R^7 is selected from the group R^{7d} consisting of H—.

In a further embodiment of the present invention R^8 is selected from the group R^{8b} consisting of

C_{3-6} -cycloalkyl, heterocyclyl and heterocyclyl- C_{1-3} -alkyl-,

wherein above mentioned C_{3-6} -cycloalkyl, heterocyclyl and heterocyclyl- C_{1-3} -alkyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 7 halogen atoms substituted C_{1-3} -alkyl-.

In a further embodiment of the present invention R^8 is selected from the group R^{8c} consisting of

C_{3-6} -cycloalkyl and heterocyclyl,

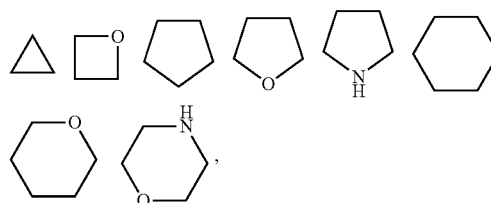
wherein above mentioned C_{3-6} -cycloalkyl and heterocyclyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 7 halogen atoms substituted C_{1-3} -alkyl-.

In a further embodiment of the present invention R^8 is selected from the group R^{8c1} consisting of

C_{3-6} -cycloalkyl and a saturated 4 to 6 membered monocyclic heterocycle containing one or two heteroatoms selected from N or O,

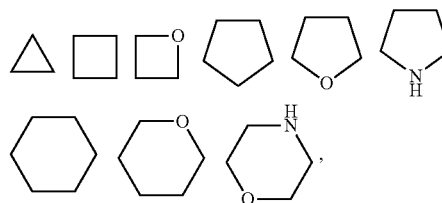
wherein above mentioned C_{3-6} -cycloalkyl and heterocyclyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 7 halogen atoms substituted C_{1-3} -alkyl-.

In a further embodiment of the present invention R^8 is selected from the group R^{8d} consisting of



wherein above mentioned groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 5 halogen atoms substituted C_{1-3} -alkyl-.

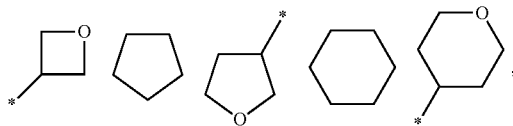
In a further embodiment of the present invention R^8 is selected from the group R^{8d1} consisting of



wherein above mentioned groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 5 halogen atoms substituted C_{1-3} -alkyl-.

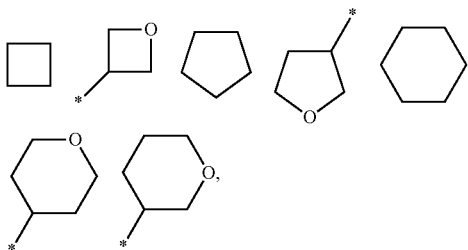
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In a further embodiment of the present invention
 R^8 is selected from the group R^{8e} consisting of



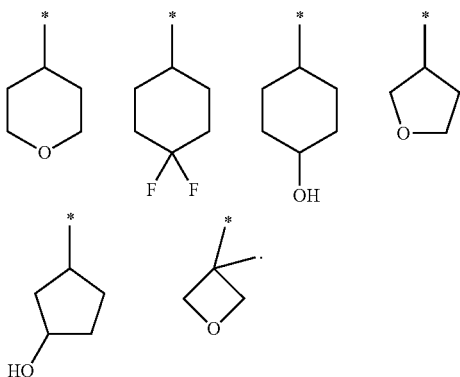
wherein above mentioned groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 3 halogen atoms substituted C_{1-3} -alkyl.

In a further embodiment of the present invention
 R^8 is selected from the group R^{8e1} consisting of

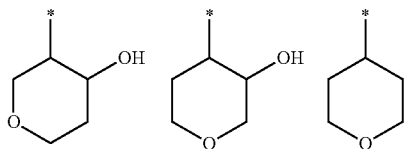


wherein above mentioned groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 3 halogen atoms substituted C_{1-3} -alkyl.

In a further embodiment of the present invention
 R^8 is selected from the group R^{8f} consisting of

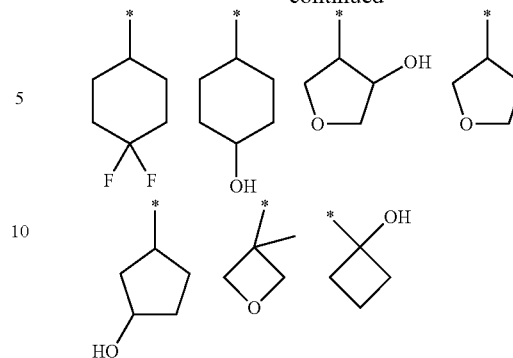


In a further embodiment of the present invention
 R is selected from the group R^{8f1} consisting of



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Each R^{1x} , R^{2x} , R^{3x} , $R^{4x/5x}$, R^{8x} , R^{7x} , R^{8x} and A^x represents a characterized, individual embodiment for the corresponding substituent as described above. Thus given the above definitions, preferred individual embodiments of the first aspect of the invention are fully characterized by the term (R^{1x} , R^{2x} , R^{3x} , $R^{4x/5x}$, R^{8x} , R^{7x} , R^{8x} and A^x), wherein for each index x an individual figure is given that ranges from “a” to the highest letter given above. All individual embodiments described by the term in parentheses with full permutation of the indices x, referring to the definitions above, shall be comprised by the present invention.

The following Table 1 shows, exemplarily and in the order of increasing preference from the first line to the last line, such embodiments E-1 to E-37 of the invention that are considered preferred. This means that embodiment E-37, represented by the entries in the last row of Table 1, is the most preferred embodiment.

TABLE 1

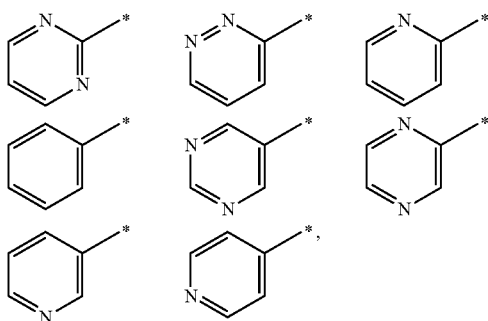
		Preferred embodiments E-1 to E-37 of the invention							
		A^x	R^{1x}	R^{2x}	R^{3x}	$R^{4x/5x}$	R^{6x}	R^{7x}	R^{8x}
40	E-1	A^b	R^{1b}	R^{2a}	R^{3b}	R^{4b}/R^{5b}	R^{6b}	R^{7b}	R^{8a}
	E-2	A^c	R^{1b}	R^{2a}	R^{3b}	R^{4b}/R^{5b}	R^{6b}	R^{7b}	R^{8a}
	E-3	A^c	R^{1c}	R^{2b}	R^{3b}	R^{4b}/R^{5b}	R^{6b}	R^{7c}	R^{8b}
	E-4	A^c	R^{1c}	R^{2b}	R^{3c}	R^{4c}/R^{5c}	R^{6b}	R^{7c}	R^{8c}
	E-5	A^c	R^{1c}	R^{2b}	R^{3c}	R^{4c}/R^{5c}	R^{6b}	R^{7d}	R^{8c}
	E-6	A^c	R^{1c}	R^{2c}	R^{3c}	R^{4c}/R^{5c}	R^{6c}	R^{7c}	R^{8c}
45	E-7	A^c	R^{1c}	R^{2d}	R^{3c}	R^{4c}/R^{5c}	R^{6c}	R^{7c}	R^{8d}
	E-8	A^d	R^{1c}	R^{2d}	R^{3d}	R^{4d}/R^{5d}	R^{6c}	—	R^{8d}
	E-9	A^e	R^{1d}	R^{2d}	R^{3d}	R^{4d}/R^{5d}	R^{6e}	—	R^{8f}
	E-10	A^e	R^{1d}	R^{2e}	R^{3d}	R^{4d}/R^{5d}	R^{6f}	—	—
	E-11	A^f	R^{1d}	R^{2d}	R^{3d}	R^{4d}/R^{5d}	R^{6e}	—	R^{8f}
	E-12	A^f	R^{1d}	R^{2e}	R^{3d}	R^{4d}/R^{5d}	R^{6f}	—	—
50	E-13	A^f	R^{1d}	R^{2f}	R^{3d}	R^{4d}/R^{5d}	R^{6e}	—	—
	E-14	A^f	R^{1d}	R^{2f}	R^{3d}	R^{4d}/R^{5d}	R^{6f}	—	—
	E-15	A^a	R^{1a}	R^{2a}	R^{3a1}	R^{4a}/R^{5a}	R^{6a}	R^{7a}	R^{8a}
	E-16	A^b	R^{1c}	R^{2c}	R^{3a1}	R^{4b}/R^{5b}	R^{6b}	R^{7b}	R^{8b}
	E-17	A^d	R^{1c}	R^{2d}	R^{3a1}	R^{4c}/R^{5c}	R^{6b}	—	R^{8c}
	E-18	A^e	R^{1c}	R^{2d}	R^{3a1}	R^{4d}/R^{5d}	R^{6b}	—	R^{8d}
55	E-19	A^g	R^{1c}	R^{2d}	R^{3a1}	R^{4d}/R^{5d}	R^{6b}	—	R^{8f}
	E-20	A^d	R^{1c}	R^{2d}	R^{3g}	R^{4d}/R^{5d}	R^{6b}	—	R^{8c1}
	E-21	A^e	R^{1c}	R^{2d}	R^{3g}	R^{4d}/R^{5d}	R^{6b}	—	R^{8d}
	E-22	A^g	R^{1c}	R^{2d}	R^{3g}	R^{4d}/R^{5d}	R^{6b}	—	R^{8f}
	E-23	A^a	R^{1a}	R^{2a1}	R^{3a}	R^{4a}/R^{5a}	R^{6a}	R^{7a}	R^{8a}
	E-24	A^b	R^{1b}	R^{2d1}	R^{3a}	R^{4c}/R^{5c}	R^{6b}	R^{7c}	R^{8b}
	E-25	A^c	R^{1c}	R^{2d1}	R^{3a}	R^{4d}/R^{5d}	R^{6c}	—	R^{8c1}
60	E-26	A^d	R^{1c}	R^{2d}	R^{3b}	R^{4d}/R^{5d}	R^{6c}	—	R^{8d1}
	E-27	A^d	R^{1c}	R^{2d1}	R^{3c}	R^{4d}/R^{5d}	R^{6d}	—	R^{8e1}
	E-28	A^d	R^{1c1}	R^{2c1}	R^{3c}	R^{4d}/R^{5d}	R^{6d}	—	R^{8f1}
	E-29	A^e	R^{1c}	R^{2d1}	R^{3b}	R^{4d}/R^{5d}	R^{6c}	—	R^{8c1}
	E-30	A^e	R^{1c}	R^{2d1}	R^{3b}	R^{4d}/R^{5d}	R^{6d}	—	R^{8d1}
	E-31	A^e	R^{1c1}	R^{2e1}	R^{3c}	R^{4d}/R^{5d}	R^{6e}	—	—
65	E-32	A^f	R^{1c}	R^{2d1}	R^{3b}	R^{4d}/R^{5d}	R^{6c}	—	R^{8e1}
	E-33	A^f	R^{1c1}	R^{2e1}	R^{3c}	R^{4d}/R^{5d}	R^{6e}	—	—

TABLE 1-continued

Preferred embodiments E-1 to E-37 of the invention								
	A ^x	R ^{1x}	R ^{2x}	R ^{3x}	R ^{4x} /R ^{5x}	R ^{6x}	R ^{7x}	R ^{8x}
E-34	A ^f	R ^{1c1}	R ^{2f1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6f}	—	—
E-35	A ^g	R ^{1c}	R ^{2c1}	R ^{3b}	R ^{4d} /R ^{5d}	R ^{6c}	—	R ^{8e1}
E-36	A ^g	R ^{1c}	R ^{2d1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6e}	—	R ^{8f1}
E-37	A ^g	R ^{1c1}	R ^{2f1}	R ^{3c}	R ^{4d} /R ^{5d}	R ^{6f}	—	—

Accordingly, for example E-15 covers compounds of formula I, wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl- and pyrazinyl- groups are substituted with R¹ and R²;

R¹ is selected from the group R^{1a} consisting of

H, halogen, NC—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— with n=0, 1, 2, 3 or 4, wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO— and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R² is selected from the group R^{2a} consisting of

H, HO—, halogen, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— with n=0, 1, 2, 3 or 4, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0, 1 or 2 and o=0, 1 or 2,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R³ is selected from the group R^{3a1} consisting of

C₃₋₆-cycloalkyl-,

wherein the above mentioned C₃₋₆-cycloalkyl-group may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC—, HO—, C₁₋₃-alkyl- and C₁₋₃-alkyl-O—;

R⁴, R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC—, HO—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cy-

cloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O—,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O— groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O—;

R⁶ is selected from the group R^{6a} consisting of

H, NC—, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O—

wherein above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of

H, carbocyclyl, heterocyclyl and heteroaryl,

wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of HO—, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-O— and halogen;

R⁸ is selected from the group R^{8a} consisting of

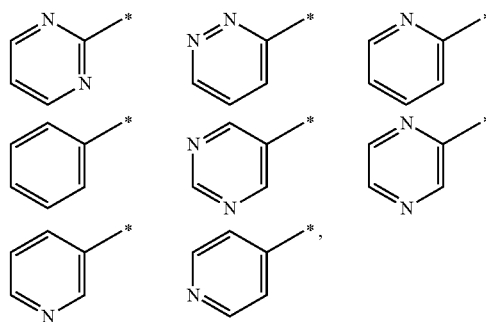
C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl,

wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-;

the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

Accordingly, for example E-23 covers compounds of formula I, wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl- and pyrazinyl- groups are substituted with R¹ and R²;

R¹ is selected from the group R^{1a} consisting of

H, halogen, NC—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— with n=0, 1, 2, 3 or 4, wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO— and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

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R² is selected from the group R^{2a1} consisting of

HO—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— with n=0, 1, 2, 3 or 4, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0, 1 or 2 and o=0, 1 or 2

wherein above mentioned C₁₋₆-alkyl- and C₁₋₆-alkyl-O— groups are substituted with 1 to 5 substituents independently selected from the group consisting of HO—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—,

and

wherein above mentioned C₁₋₆-alkyl- and C₁₋₆-alkyl-O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

wherein above mentioned C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R³ is selected from the group R^{3a} consisting of

H, halogen, NC—, C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-, wherein the above mentioned C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC—, HO—, C₁₋₃-alkyl- and C₁₋₃-alkyl-O—;

R⁴, R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC—, HO—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O—, wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O— groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C₁₋₂-alkyl-, and optionally with 1 to 5 halogen atoms substituted C₁₋₂-alkyl-O—;

R⁶ is selected from the group R^{6a} consisting of

H, NC—, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O— wherein above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of

H, carbocyclyl, heterocyclyl and heteroaryl, wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of HO—, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-, optionally with 1 to 3 halogen atoms substituted C₁₋₄-alkyl-O— and halogen;

R⁸ is selected from the group R^{8a} consisting of

C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl,

24

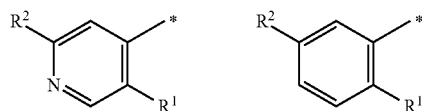
wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-;

the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

Accordingly, for example E-29 covers compounds of formula I,

wherein

A is selected from the group A^e consisting of



R¹ is selected from the group R^{1c} consisting of

H, H₃C—, F₃C—, F₂HC—, FH₂C—, fluorine, chlorine and bromine;

R² is selected from the group R^{2d1} consisting of

HO—, C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, a saturated 5 or 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸—(CH₂)_n—O— with n=0, 1 or 2, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m=0 or 1 and o=0 or 1

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups are substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of HO—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—,

and

wherein above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-,

and

wherein above mentioned C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, saturated 5 or 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5, preferably 1 to 3, substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R³ is selected from the group R^{3b} consisting of

H, C₁₋₃-alkyl-, cyclobutyl- and cyclopropyl-,

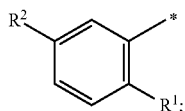
wherein the above mentioned C₁₋₃-alkyl-, cyclobutyl-, and cyclopropyl-groups may optionally be substituted with 1 to 7 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl-O—, NC— and HO—;

25

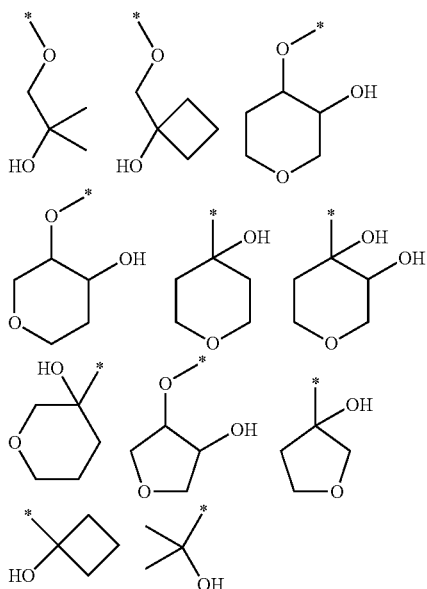
R^4, R^5 are selected from the group R^{4d}/R^{5d} consisting of
H;
 R^6 is selected from the group R^{6c} consisting of
H and C_{1-2} -alkyl-,
wherein above mentioned C_{1-2} -alkyl- group may optionally be substituted with 1-5 fluorine and/or chlorine atoms;
 R^8 is selected from the group R^{8c1} consisting of
 C_{3-6} -cycloalkyl and a saturated 4 to 6 membered monocyclic heterocycle containing one or two heteroatoms selected from N or O,
wherein above mentioned C_{3-6} -cycloalkyl and heterocycl-
yl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and optionally with 1 to 7 halogen atoms substituted C_{1-3} -alkyl-;
the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

Accordingly, for example E-37 covers compounds of formula I,
wherein

A is selected from the group A^9 consisting of



R^1 is selected from the group R^{1c1} consisting of
 H_3C —, fluorine and chlorine;
 R^2 is selected from the group R^{2f1} consisting of



R^3 is selected from the group R^{3c} consisting of
H, and H_3C — and cyclopropyl-,
wherein the above mentioned H_3C — and cyclopropyl- groups may optionally be substituted with 1 to 3 fluorine atoms;

26

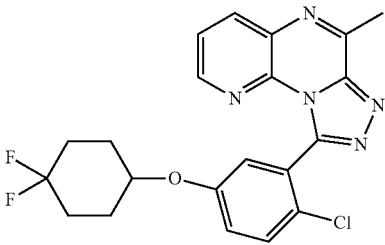
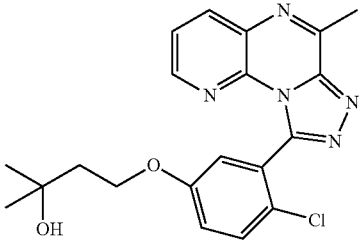
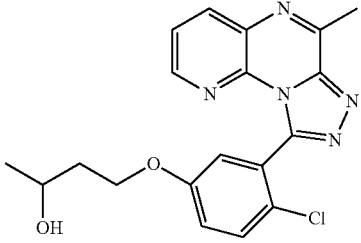
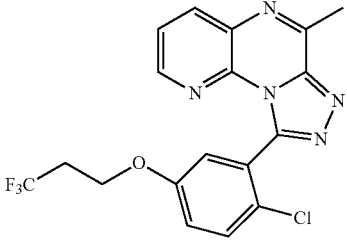
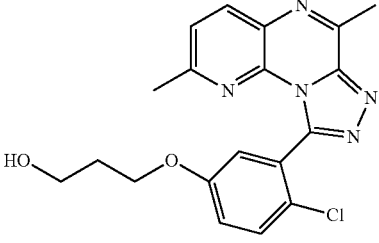
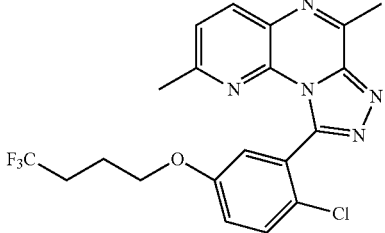
R^4, R^5 are selected from the group R^{4d}/R^{5d} consisting of
H;
 R^6 is selected independently of each other from the group R^{6f} consisting of
 H_3C —;
the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

Further preferred are the following compounds listed in table 2:

No.	Structure
I	
20	
25	
II	
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35	
III	
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IV	
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55	
V	
60	

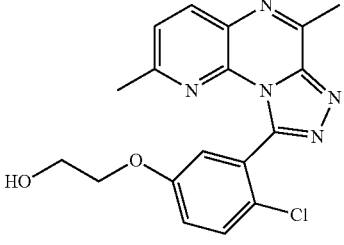
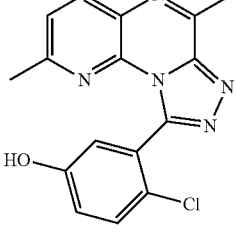
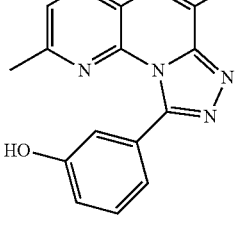
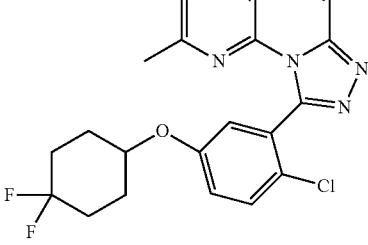
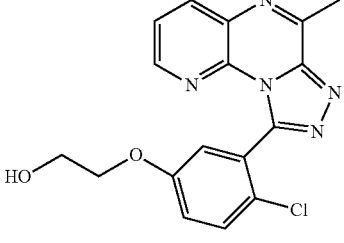
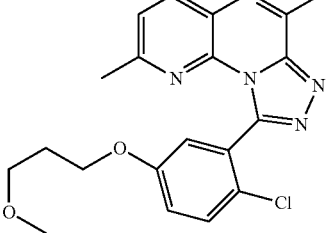
27

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No.	Structure
VI	
VII	
VIII	
IX	
X	
XI	

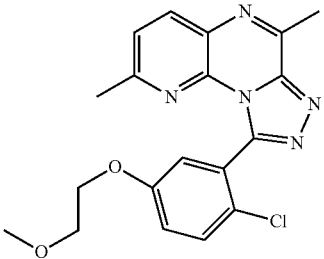
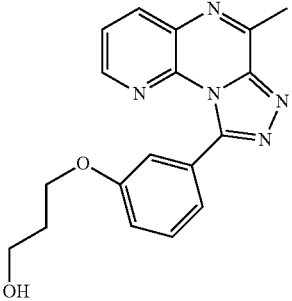
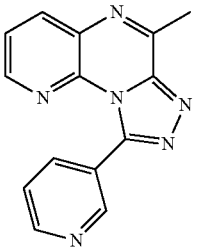
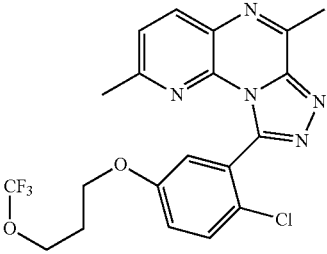
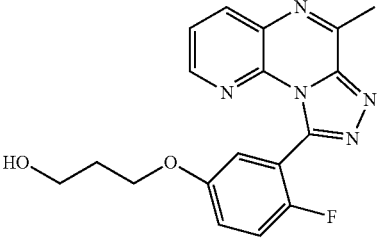
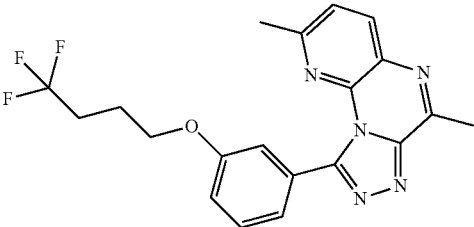
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No.	Structure
5 XII	
10 XIII	
15 XIV	
20 XV	
25 XVI	
30 XVII	

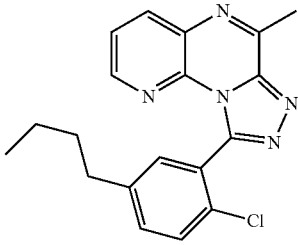
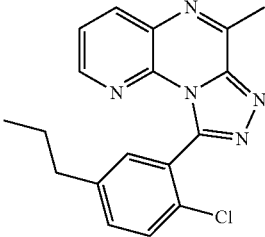
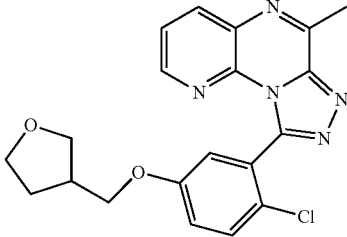
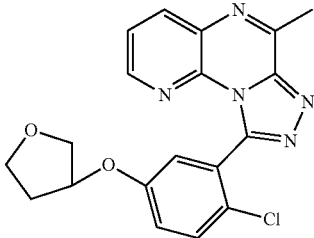
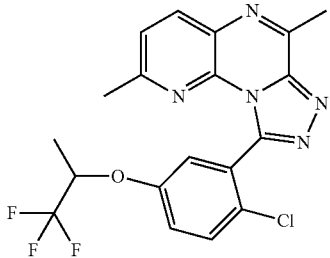
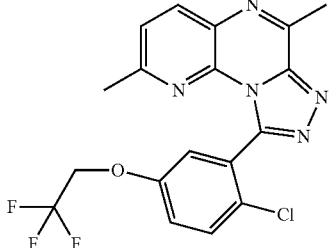
29

-continued

No.	Structure
XVIII	
XIX	
XX	
XXI	
XXII	
XXIII	

30

-continued

No.	Structure
5 XXIV	
10	
15 XXV	
20	
25 XXVI	
30	
35 XXVII	
40	
45 XXVIII	
50	
55 XXIX	
60	
65	

31

-continued

No.	Structure
XXX	
XXXI	
XXXII	
XXXIII	
XXXIV	

32

-continued

No.	Structure
5 XXXV	
10	
15 XXXVI	
20	
25 XXXVII	
30	
35 XXXVIII	
40	
45	
XXXIX	
50	
55	
XL	
60	
65	

33

-continued

No.	Structure
XLI	
XLII	
XLIII	
XLIV	
XLV	
XLVI	

34

-continued

No.	Structure
5 XLVII	
10	
15 XLVIII	
20	
25 XLIX	
30	
35 L	
40	
45 LI	
50	
55 LII	
60	
65	

35

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No.	Structure
LIII	
LIV	
LV	
LVI	
LVII	
LVIII	

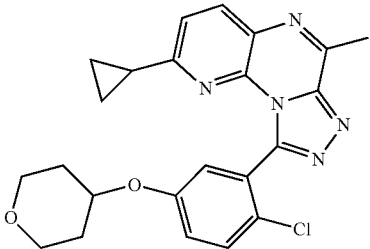
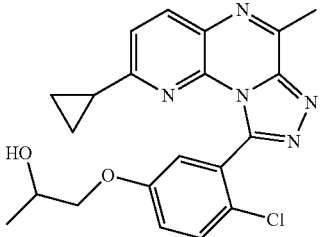
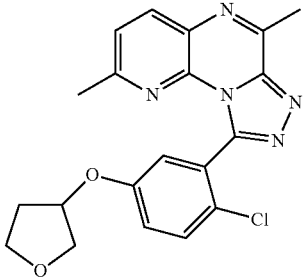
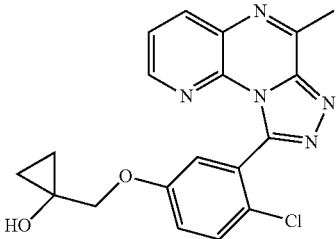
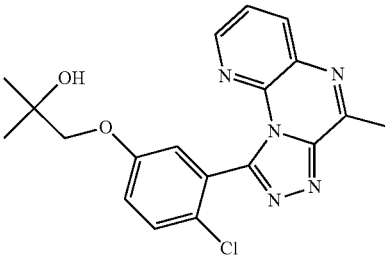
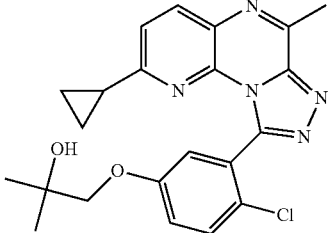
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No.	Structure
5 LIX	
10	
15 LX	
20	
25 LXI	
30	
35 LXII	
40	
45 LXIII	
50	
55	
60 LXIV	
65	

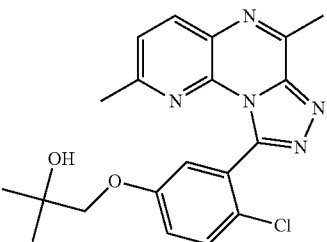
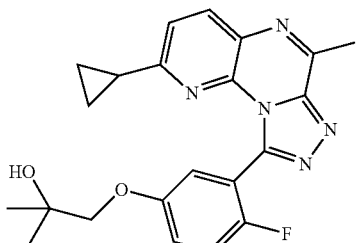
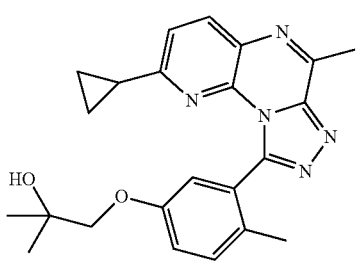
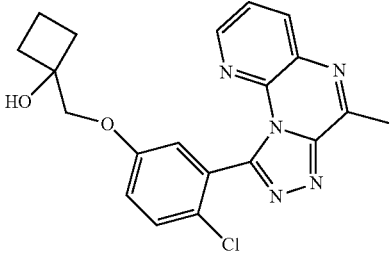
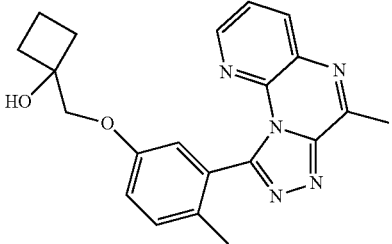
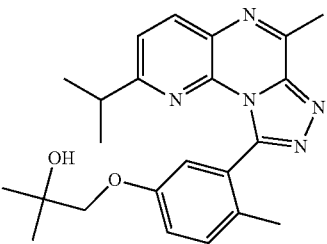
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No.	Structure
LXV	
LXVI	
LXVII	
LXVIII	
LXIX	
LXX	

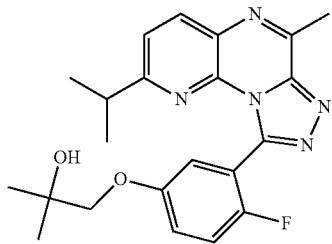
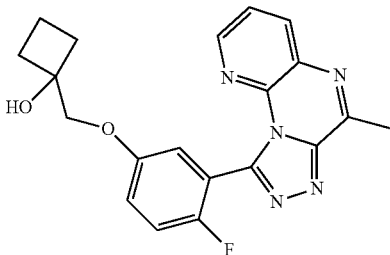
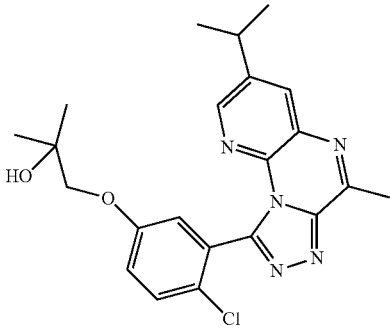
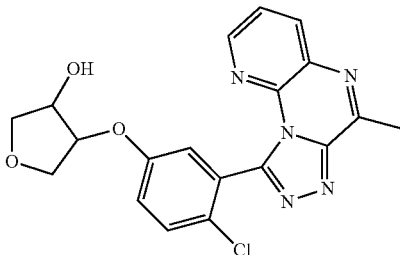
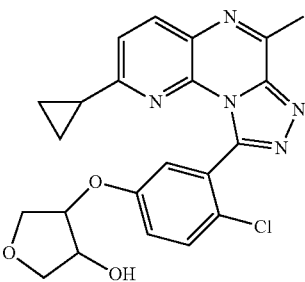
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No.	Structure
5 LXXI	
10 LXXII	
15 LXXIII	
20 LXXIV	
25 LXXV	
30 LXXVI	

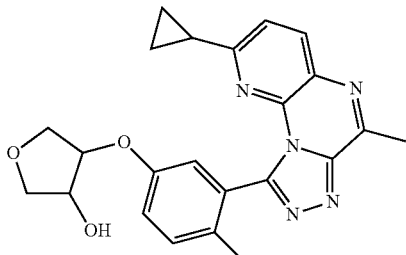
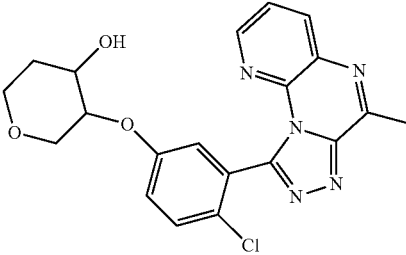
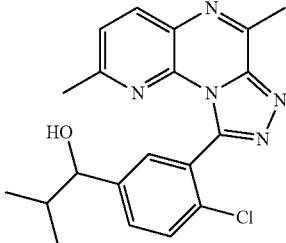
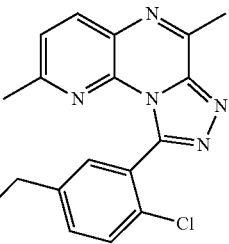
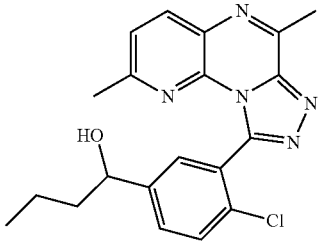
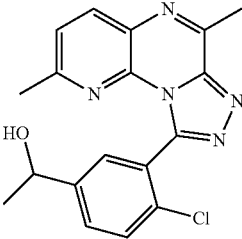
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No.	Structure
LXXVII	
LXXVIII	
LXXIX	
LXXX	
LXXXI	

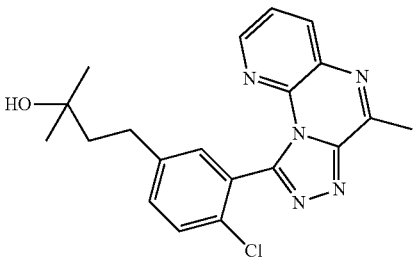
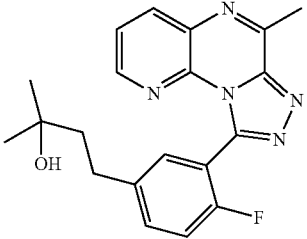
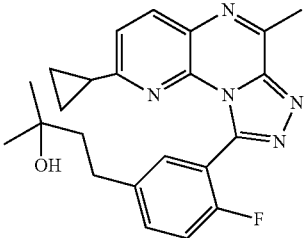
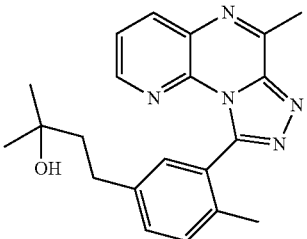
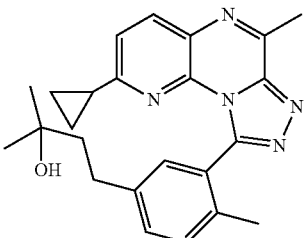
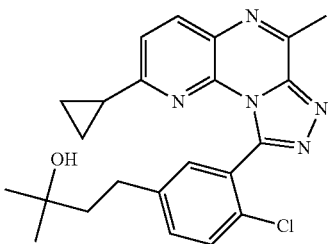
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No.	Structure
5 LXXXII	
10	
15 LXXXIII	
20	
25 LXXXIV	
30	
35 LXXXV	
40	
45 LXXXVI	
50	
55 LXXXVII	
60	
65	

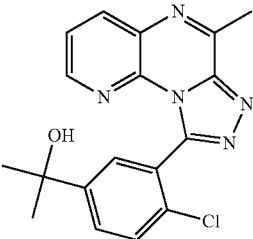
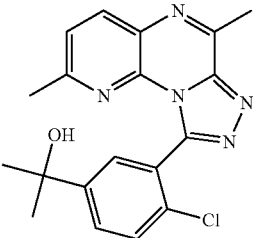
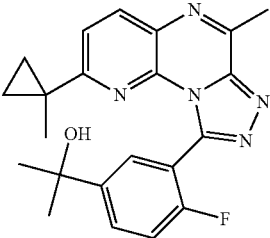
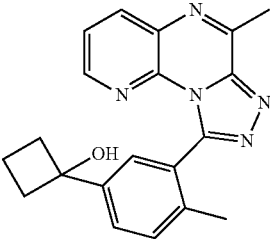
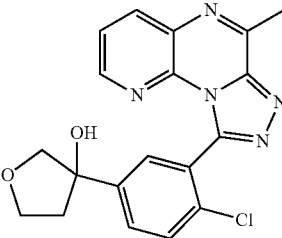
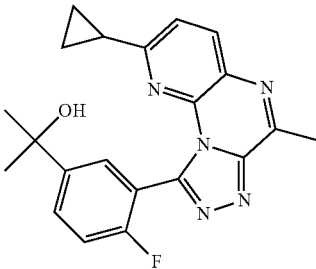
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No.	Structure
LXXXVIII	
LXXXIX	
XC	
XCI	
XCII	
XCIII	

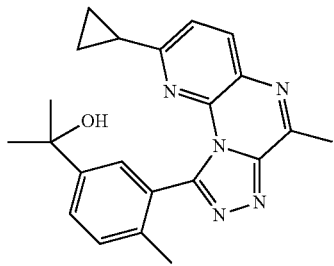
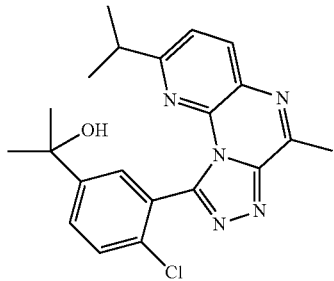
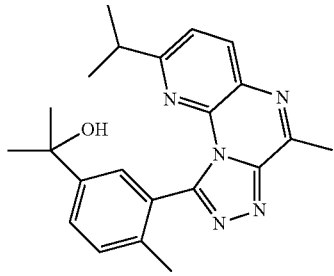
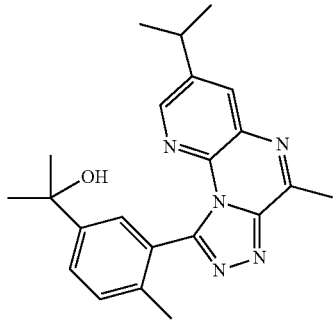
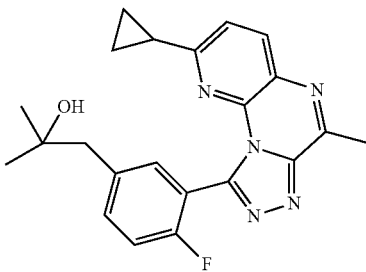
42

-continued

No.	Structure
5 XCIV	
10	
15 XCV	
20	
25 XCVI	
30	
35 XCVII	
40	
45 XCVIII	
50	
55	
60 XCIX	
65	

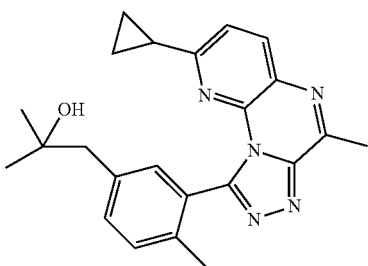
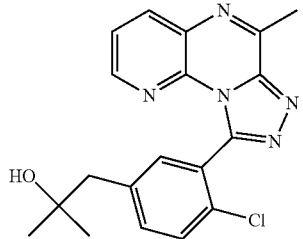
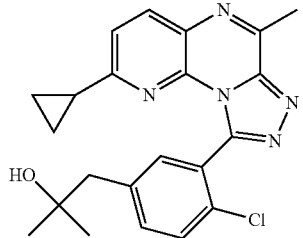
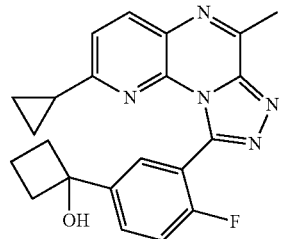
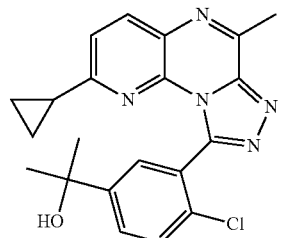
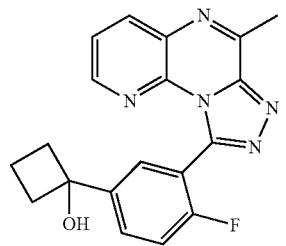
43

-continued

No.	Structure
C	
CI	
CII	
CIII	
CIV	

44

-continued

No.	Structure
5 CV	
10	
15	
CVI	
20	
25	
CVII	
30	
35	
CVIII	
40	
45	
CIX	
50	
55	
CX	
60	
65	

45

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No.	Structure
CXI	
CXII	
CXIII	
CXIV	
CXV	
CXVI	

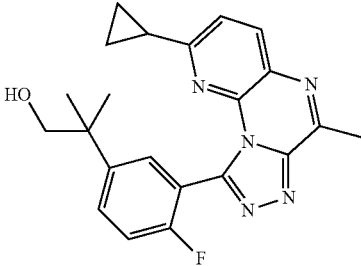
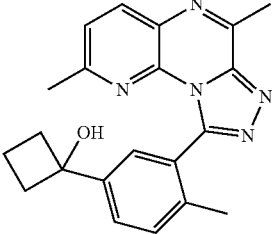
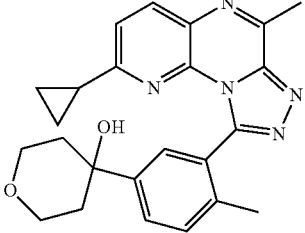
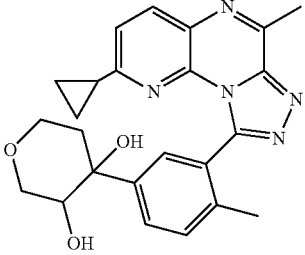
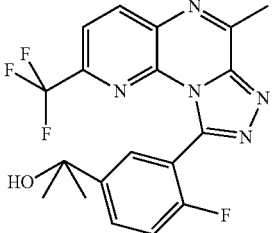
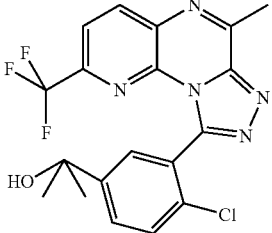
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No.	Structure
5 CXVII	
10	
15 CXVIII	
20	
25	
30 CXIX	
35	
40 CXX	
45	
50 CXXI	
55	
60 CXXII	
65	

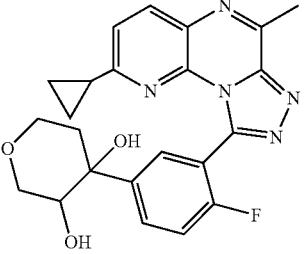
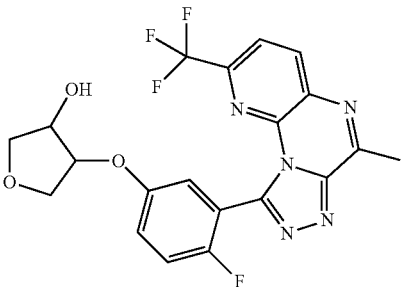
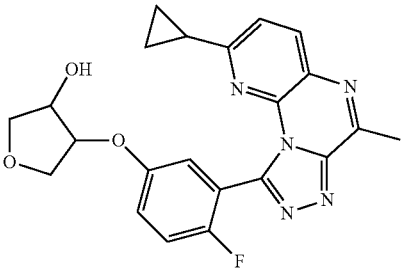
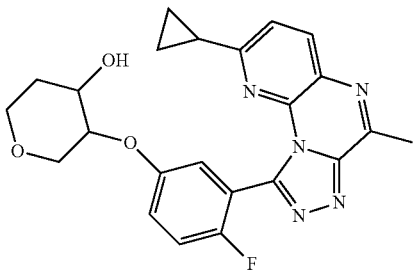
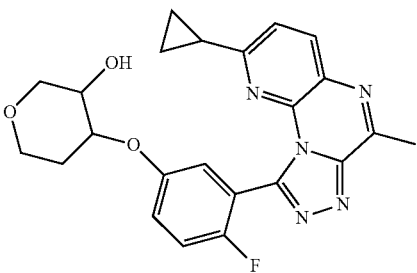
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No.	Structure
CXXIII	
CXXIV	
CXXV	
CXXVI	
CXXVII	
CXXVIII	

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-continued

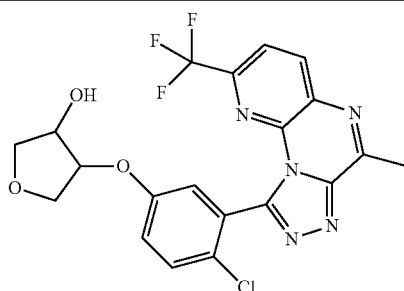
No.	Structure
CXXIX	
CXXX	
CXXXI	
CXXXII	
CXXXIII	

49

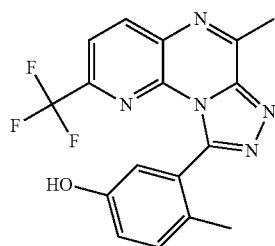
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No.	Structure
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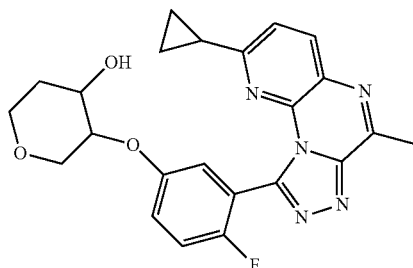
CXXXIV



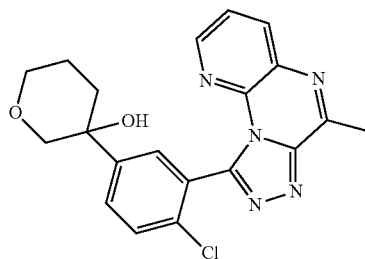
CXXXV



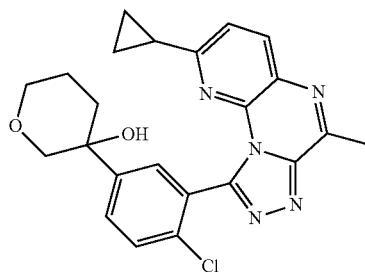
CXXXVI



CXXXVII



CXXXVIII

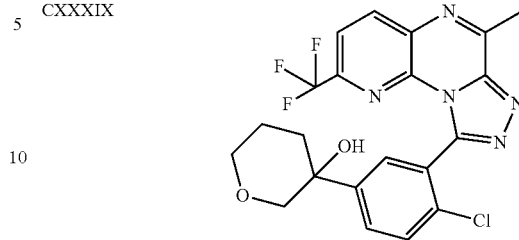


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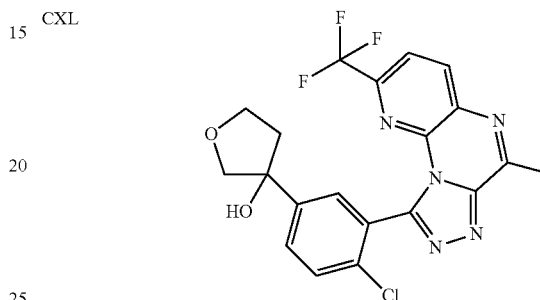
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No.	Structure
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CXXXIX



CXL

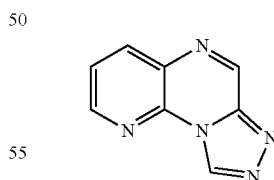


the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the salts thereof.

Some terms used above and hereinafter to describe the compounds according to the invention will now be defined more closely.

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to. In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example C₁₋₆-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C₁₋₃-alkyl-" means an aryl group which is bound to a C₁₋₃-alkyl group, the latter of which is bound to the core molecule or to the group to which the substituent is attached.

Within the present invention, the term "core molecule" is defined by the following structure:



In general, the attachment site of a given residue to another group shall be variable, i.e. any capable atom, bearing hydrogens to be replaced, within this residue may be the linking spot to the group being attached, unless otherwise indicated.

In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail.

An asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule or to the substituent to which it is bound as defined.

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Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc. . . .) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

The phrase "pharmaceutically acceptable" or "physiologically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" or "physiologically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts or physiologically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2', 2"-nitritoltris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2,2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pantoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglyutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like (also see Pharmaceutical salts, Berge, S. M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the

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free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts) also comprise a part of the invention.

The term "substituted" as used herein means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's viable valence number is not exceeded, and that the substitution results in a stable compound.

The term "partially unsaturated" as used herein means that in the designated group or moiety 1, 2, or more, preferably 1 or 2, double bonds are present. Preferably, as used herein, the term "partially unsaturated" does not cover fully unsaturated groups or moieties.

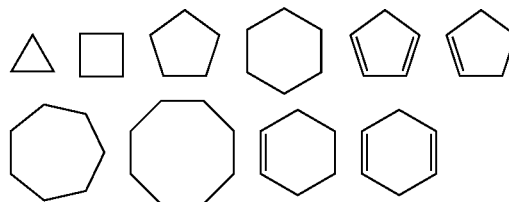
Terms like "... optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—" or "... optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl—" in a section like "... groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-O—, and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl—" means that the referenced group may be substituted with 1 to 5 substituents, wherein these substituents can be halogen, HO—, C₁₋₃-alkyl-O— which may be optionally fluorinated with 1 to 7 fluoro atoms, and C₁₋₃-alkyl-O— which may be optionally fluorinated with 1 to 7 fluoro atoms.

The term "halogen" generally denotes fluorine, chlorine, bromine and iodine.

The term "C_{1-n}-alkyl", wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C₁₋₅-alkyl embraces the radicals H₃C—, H₃C—CH₂—, H₃C—CH₂—CH₂—, H₃C—CH(CH₃)—, H₃C—CH₂—CH₂—CH₂—, H₃C—CH₂—CH(CH₃)—, H₃C—CH(CH₃)—CH₂—, H₃C—C(CH₃)₂—, H₃C—CH₂—CH₂—CH₂—CH₂—, H₃C—CH₂—CH₂—CH(CH₃)—, H₃C—CH₂—CH(CH₃)—CH₂—, H₃C—CH(CH₃)—CH₂—CH₂—, H₃C—CH₂—C(CH₃)₂—, H₃C—C(CH₃)₂—CH₂—, H₃C—CH(CH₃)—CH(CH₃)— and H₃C—CH₂—CH(CH₂CH₃)—.

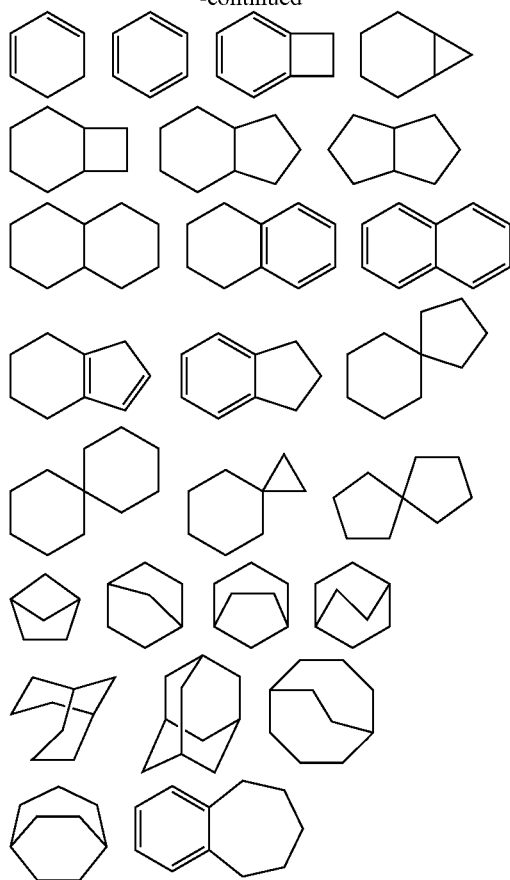
The terms "carbocyclyl" and "carbocyclic" as used either alone or in combination with another radical, mean, if not mentioned otherwise, a mono- bi- or tricyclic ring structure consisting of 3 to 14 carbon atoms. The terms, if not mentioned otherwise, refers to fully saturated, partially saturated and aromatic ring systems. The terms encompass fused, bridged and spirocyclic systems.

Thus, the terms include the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:



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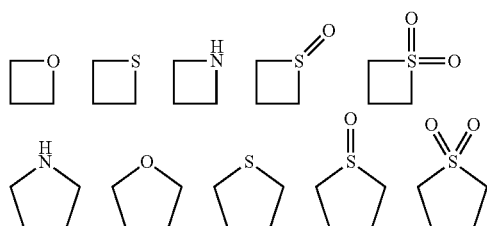
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The term “C_{3-n}-cycloalkyl”, wherein n is an integer from 4 to n, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C atoms. For example the term C₃₋₇-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

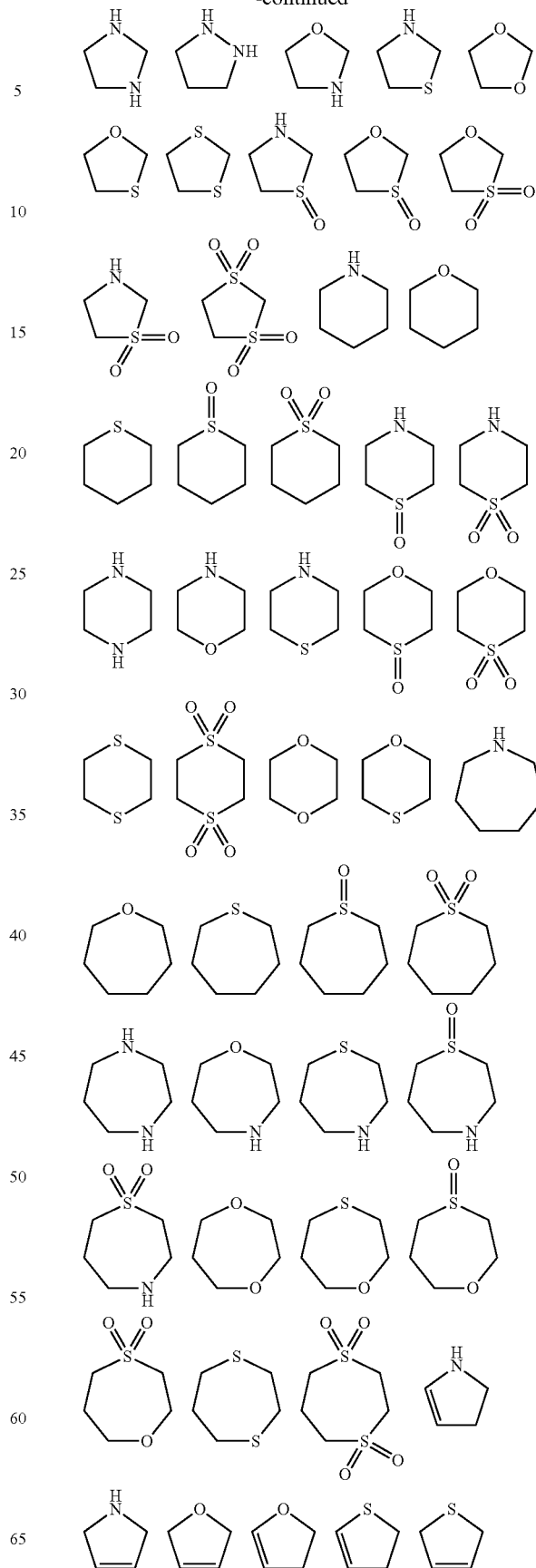
The terms “heterocyclyl” and “heterocycle” as used either alone or in combination with another radical, mean a saturated or unsaturated mono- or polycyclic ring system containing one or more heteroatoms selected from N, O or S(O)_r, wherein r=0, 1 or 2, which may contain aromatic rings consisting of, if not mentioned otherwise, 3 to 14 ring atoms wherein none of the heteroatoms is part of an aromatic ring. The terms encompass fused, bridged and spirocyclic systems. The terms are intended to include all the possible isomeric forms.

Thus, the terms include the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:



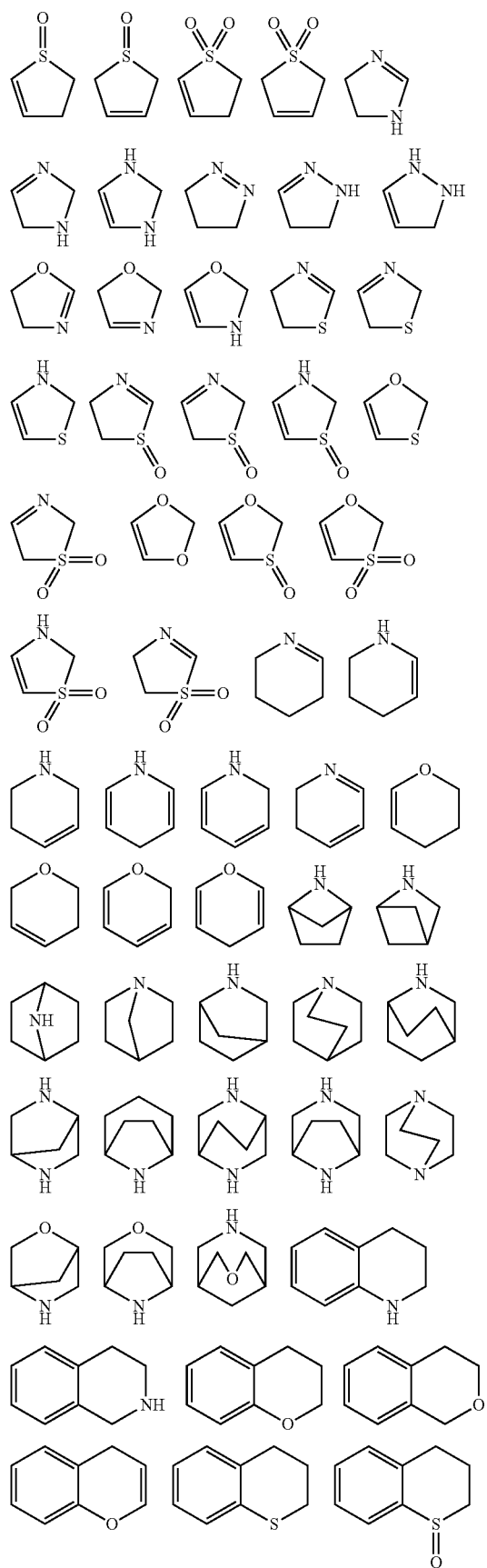
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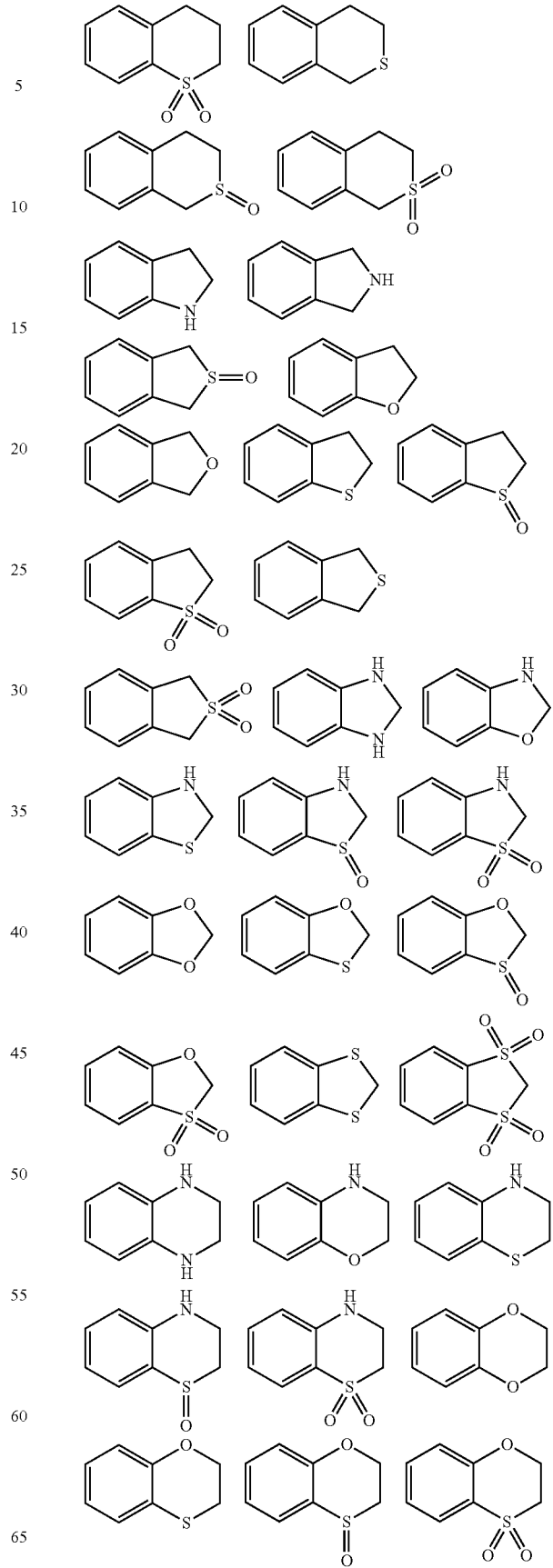


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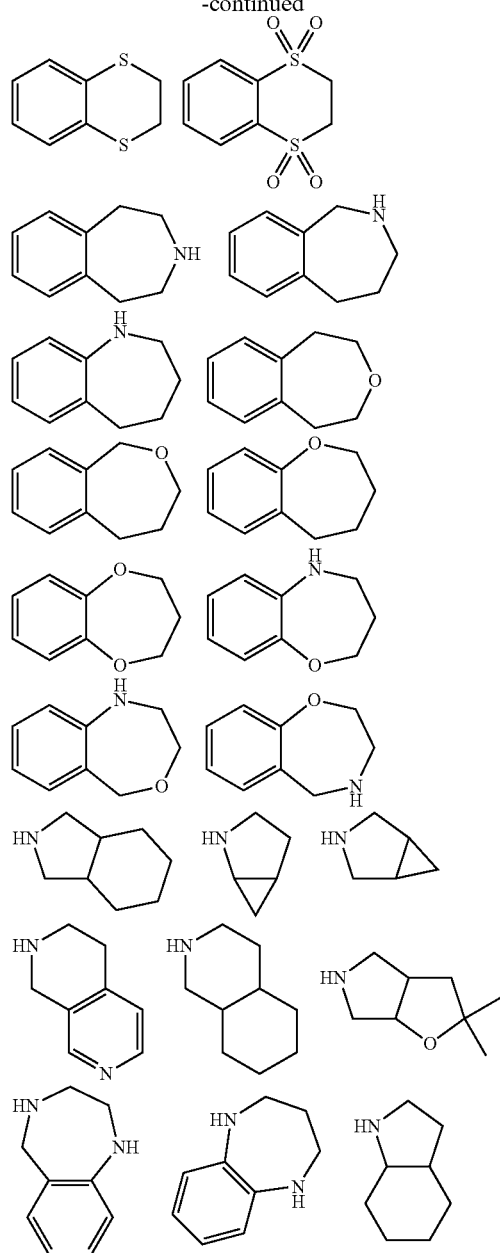
**56**

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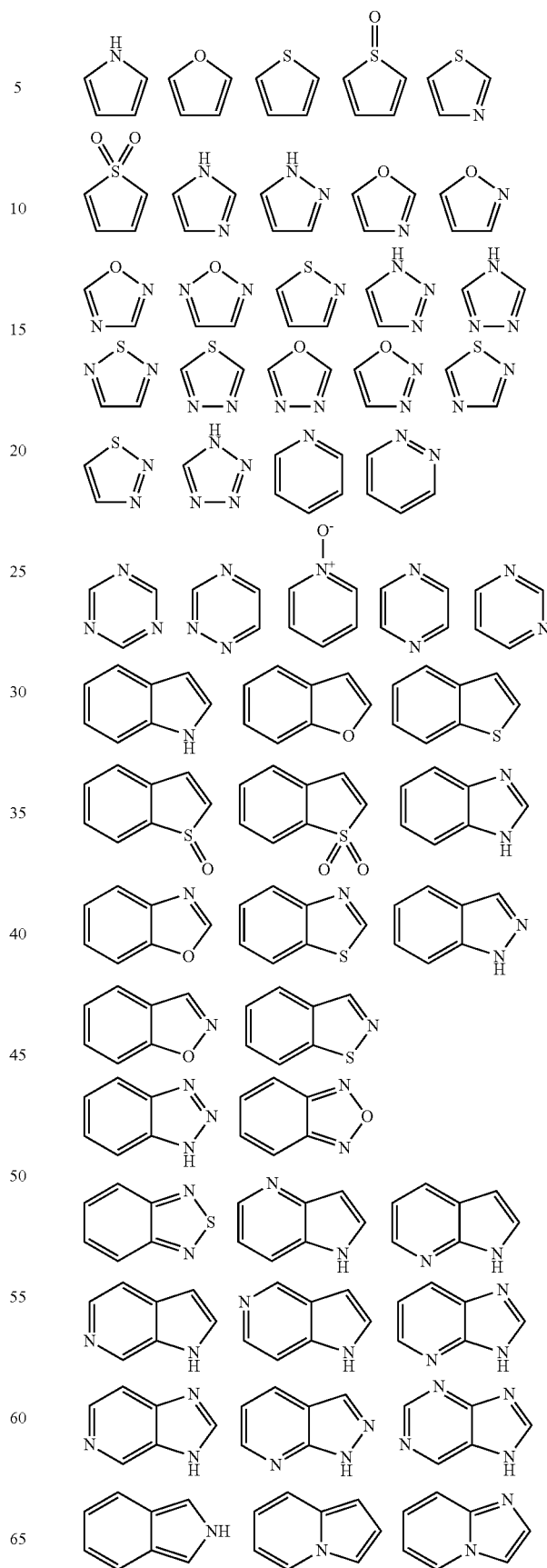


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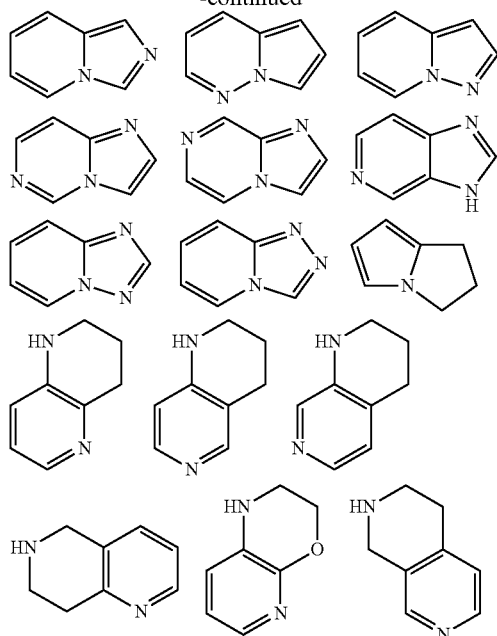


The term "aryl" as used herein, either alone or in combination with another radical, denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl.

The term "heteroaryl" means a mono- or polycyclic-ring systems containing one or more heteroatoms selected from N, O or S(O)_r, wherein r=0, 1 or 2, consisting of 5 to 14 ring atoms wherein at least one of the heteroatoms is part of an aromatic ring. The term "heteroaryl" is intended to include all the possible isomeric forms. Thus, the term "heteroaryl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:

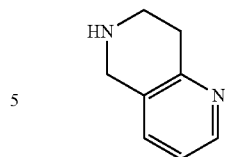
59

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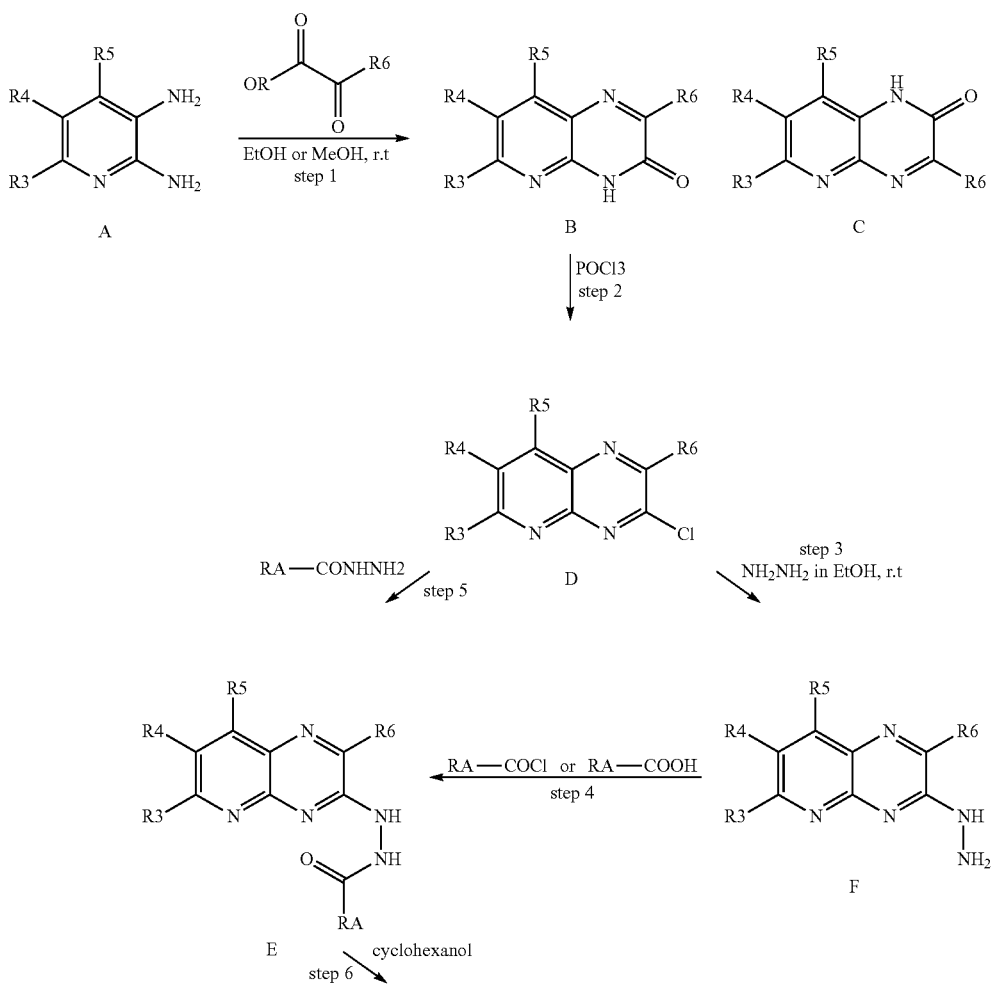
Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

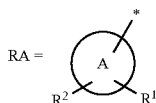
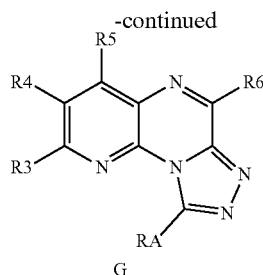
The compounds according to the invention may be obtained using methods of synthesis known in principle. Preferably, the compounds are obtained by the following methods according to the invention which are described in more detail hereinafter.

Preparation

The following schemes illustrate generally how to manufacture the compounds of the present invention by way of example. The abbreviated substituents may be as defined above if not defined otherwise within the context of the schemes:

Scheme 1:





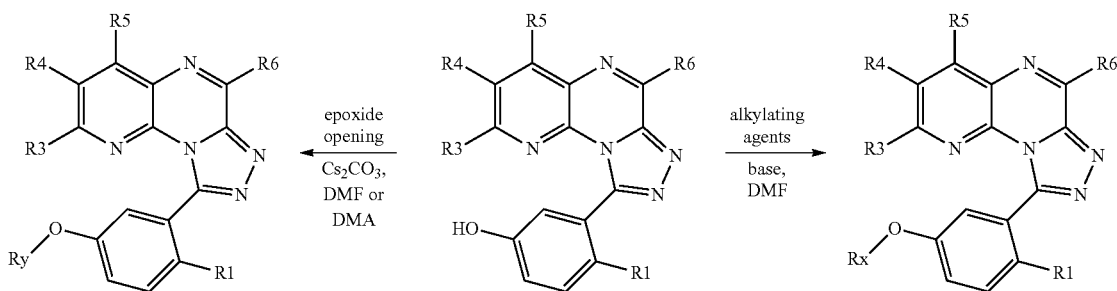
Scheme 1: In a first step, substituted 1,2-pyrido-diamines (A), commercially available or prepared following well known reported procedures, were reacted with the appropriate 1,2 - keto ester or acid in EtOH or MeOH as solvents at room temperature, to form the corresponding pyrido[2,3-b] pyrazinone intermediates (B,C). Where required, regioisomers were separated by flash chromatography and treated with POCl₃ under heating to obtain the 2-chloro-pyridopyrazines(D).

Nucleophilic substitution was performed using hydrazine hydrate in appropriate solvents (e.g. EtOH) at room temperature to form the corresponding pyrido[2,3-b]-pyrazin-3-yl-
 idrazines derivatives (F). Reaction with appropriate acyl
 chlorides or carboxylic acids in the presence of a coupling
 agent (e.g. HATU or TBTU) and a base (e.g. TEA or DIPEA),
 gave the corresponding hydrazides (E) which were submitted
 to in situ cyclization to triazoles core by heating in appropri-
 ate solvent (e.g. cyclohexanol).

Alternatively, in step 5, preformed hydrazides derivative
 were reacted with 2-chloro-pyridopyrazines (D) in appropri-
 ate solvents (such as DMF) to gave intermediates hydrazides
 (E) which were then converted to compounds G as described
 before or heating directly the 2-chloro-pyridopyrazines (D)
 with the appropriate hydrazides in appropriate solvent such as
 cyclohexanol at high temperature.

Further examples of the present invention were prepared
 following Scheme 2:

Scheme 2:

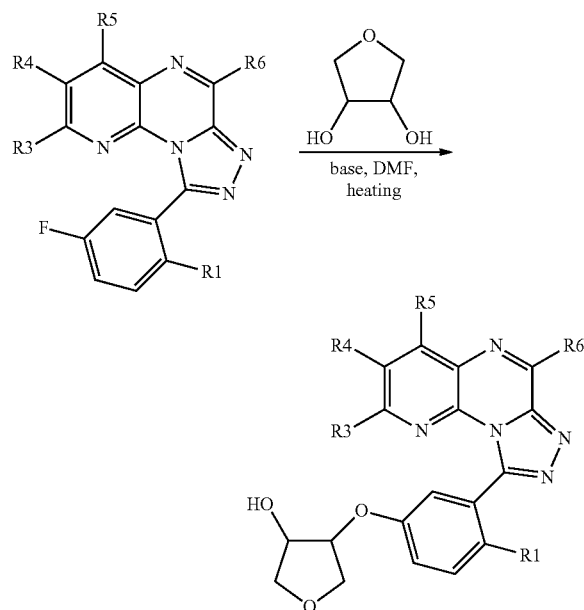


Further examples of the present invention were prepared
 by alkylation of the appropriate phenol derivative (obtained
 as described in Scheme 1) with alkylating agents (e.g. chlo-
 ride, bromide or tosylates derivatives) in the presence of a
 suitable base (e.g. tBuOK or Cs₂CO₃) in a solvent like DMF
 under heating or by ring opening of the appropriate epoxides
 in the presence of a suitable base (e.g. Cs₂CO₃) in a solvent
 like DMF or DMA under conventional heating or microwave
 irradiation.

Rx and Ry: Examples 13, 15, 16, 17, 18, 19, 20, 21, 22, 23,
 24, 25, 26, 27, 28, 29, 30, 31, 32, 32a, 33, 34, 35, 35a, 36, 37,
 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54,
 55, 56, 57, 58, 106, 107, 108a, 108b, 108c, 108d, 109a, 109b,
 109c, 109d, 110b, 110d, 111 were prepared following the
 above described procedures.

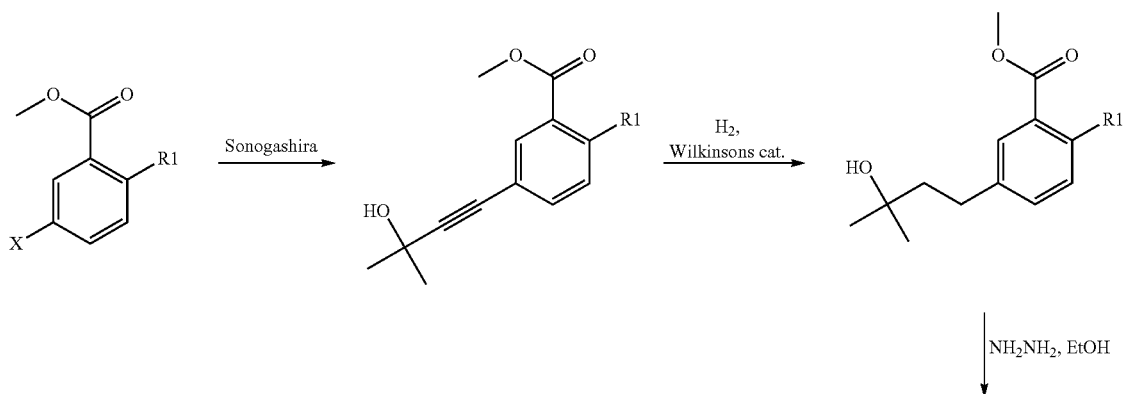
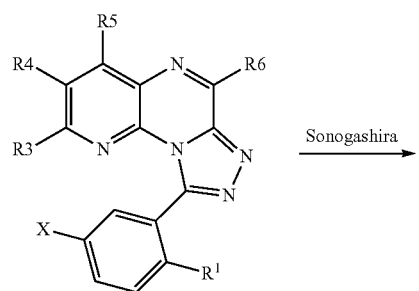
63

Scheme 3:



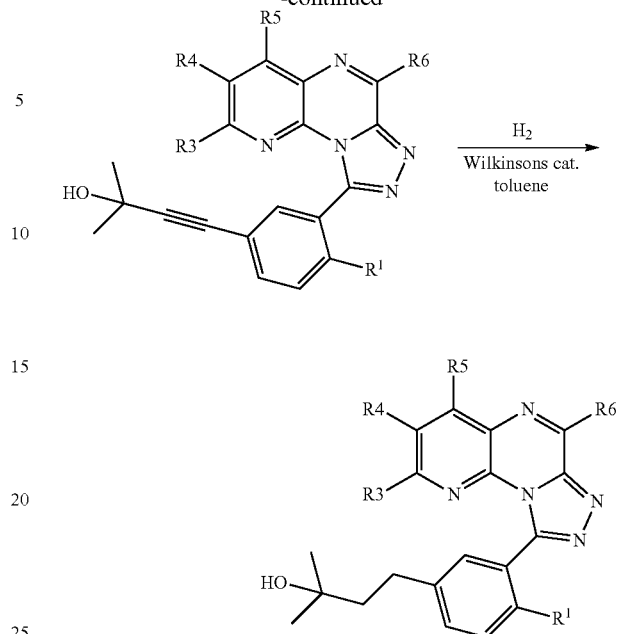
Further examples of the present invention were prepared by aromatic nucleophilic substitution, reacting the appropriate aromatic fluoro derivatives (prepared as described in Scheme 1) with primary or secondary alcohols in the presence of a suitable base (e.g. tBuOK or Cs₂CO₃), in a solvent like DMF under heating. Examples 58a, 58b, 58c were prepared following the above described procedure.

Scheme 4:



64

-continued



Further examples of the present invention were prepared by well-known cross coupling reaction (i.e. Sonogashira, see for example Organic Letters, 2007, vol. 9, p. 4057-4060) starting from appropriate aromatic halogen intermediates (X=Br,I).

The resulting unsaturated triple bond intermediates were then converted to final compounds by appropriate reduction with Wilkinson's catalyst RhCl(TPP)₃ under hydrogen atmosphere in toluene as solvent.

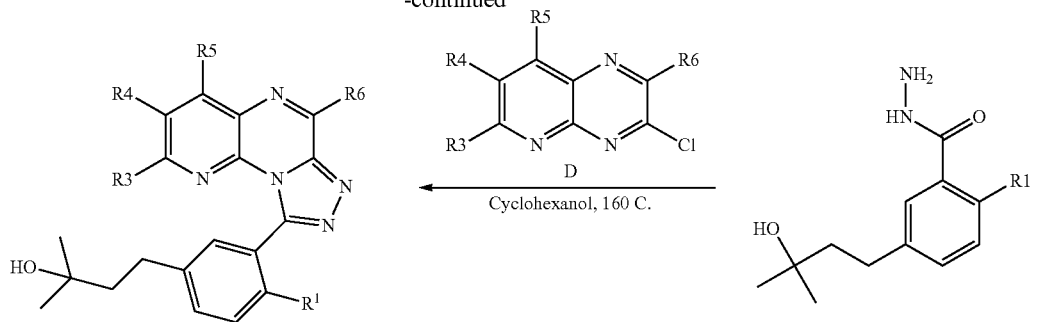
Examples 66, 67, 68, 69 were prepared following the above described procedure. Alternatively, the same synthetic approach was applied for the preparation of preformed hydrazides which were then reacted with intermediate D as described in Scheme 1

Scheme 5

65

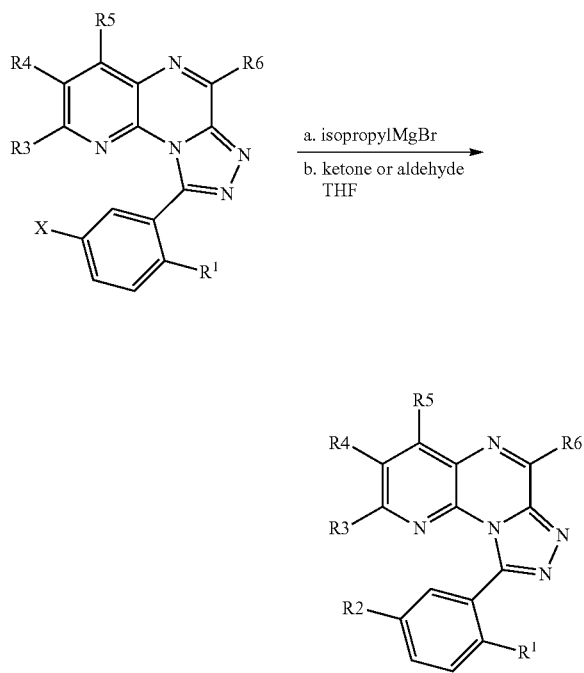
66

-continued

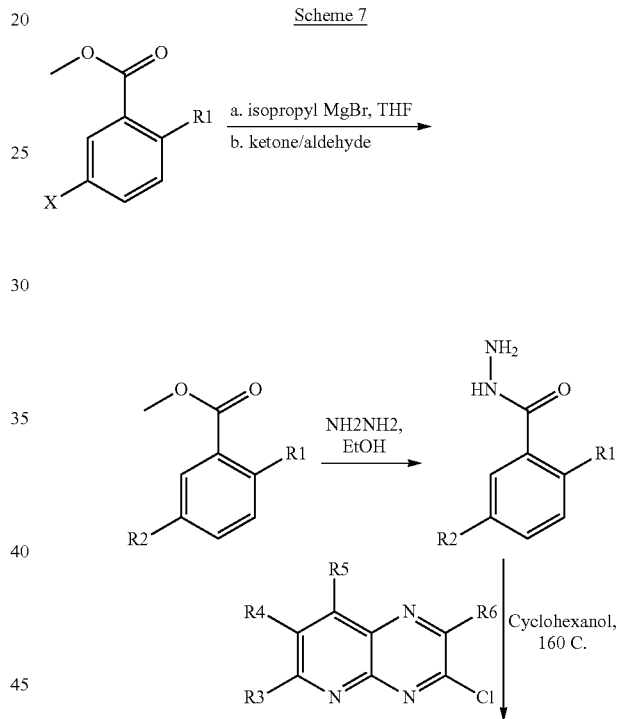


Examples 64 and 65 were prepared following the above described procedure.

Scheme 6:



Scheme 7



Further examples of the present invention were prepared as described in Scheme 6: in a first step the appropriate aromatic alogen derivatives (X=I) was treated with isopropyl magnesium bromide in a suitable solvent (like THF) at low temperature followed by addition of the appropriate ketone or aldehyde derivatives.

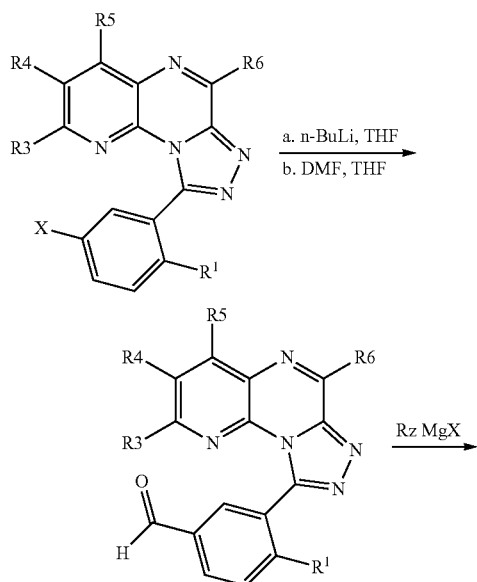
Examples 70, 71, 72, 73, 74 were prepared following the above described procedure.

Alternatively, the same synthetic approach was applied for the preparation of preformed hydrazides which were then reacted with intermediate D as described in Scheme 1.

Examples 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 96a, 96b, 96c, 97 were prepared following the above described procedure.

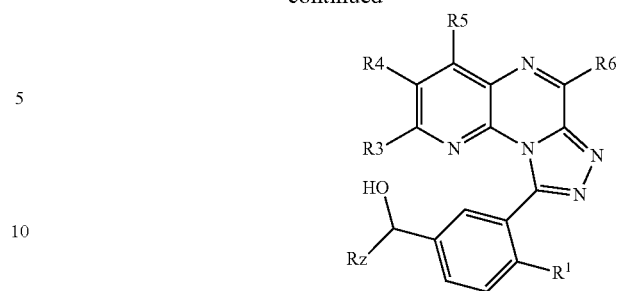
67

Scheme 8:



68

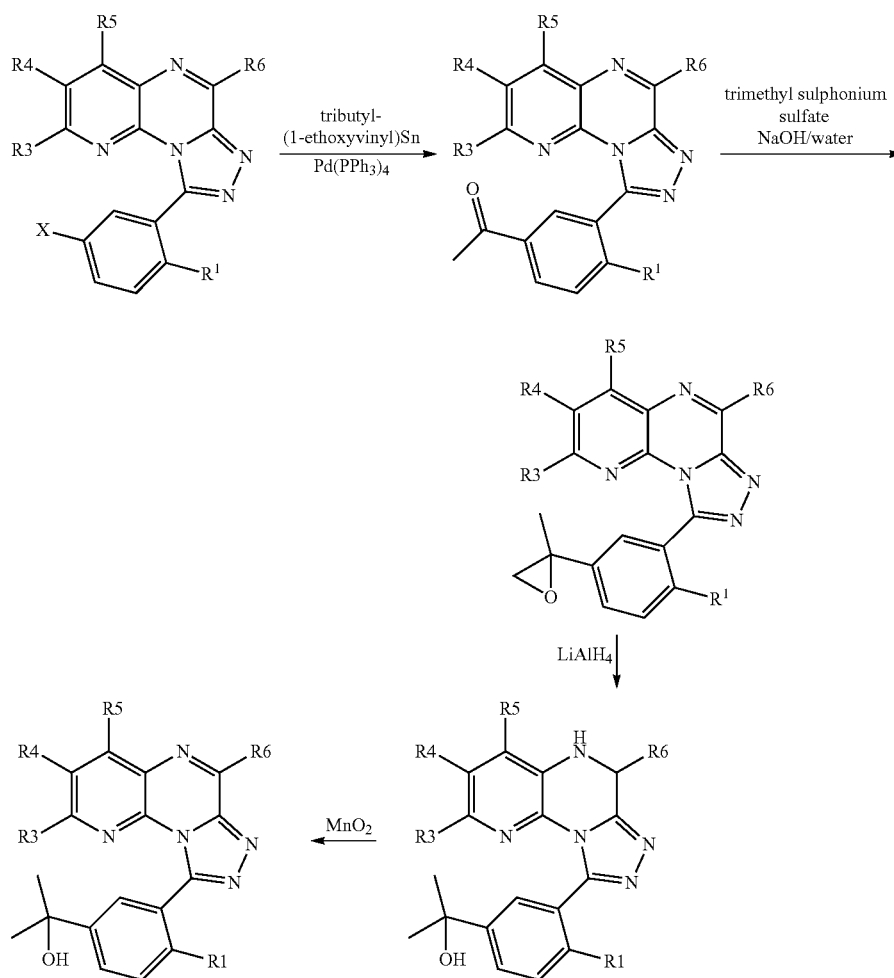
-continued



15 Further examples of the present invention were prepared as
 described in Scheme 8: in a first step the appropriate aromatic
 aldehyde is obtained by reaction of alogen derivatives ($\text{X}=\text{I}$)
 with n-BuLi in a suitable solvent (like THF) at low tempera-
 20 ture followed by addition of dry DMF in THF. In a second step
 the suitable commercially available Grignard reagent is
 added at low temperature.

Rz: Examples 59, 61, 62, 63 were prepared following the
 above reported procedure.

Scheme 9



69

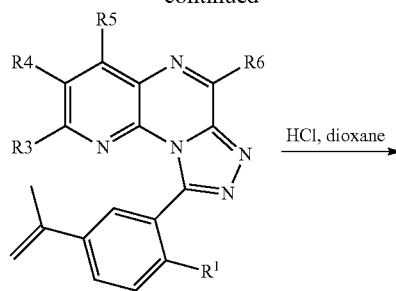
Further examples of the present invention were prepared as described in Scheme 9: in a first step the appropriate ketone is obtained by reaction of alogen derivatives (X=I,Br) with tributyl-(1-ethoxyvinyl)-tin in the presence of Pd(PPh₃)₄. The epoxide obtained by reaction with appropriate trimethyl sulphonium ylide was then subjected to ring opening with hydride and subsequent oxidation with suitable agents such as manganese dioxide in appropriate solvents (DCM).

Examples 76, 77, 78, 79 were prepared following the above reported procedure.

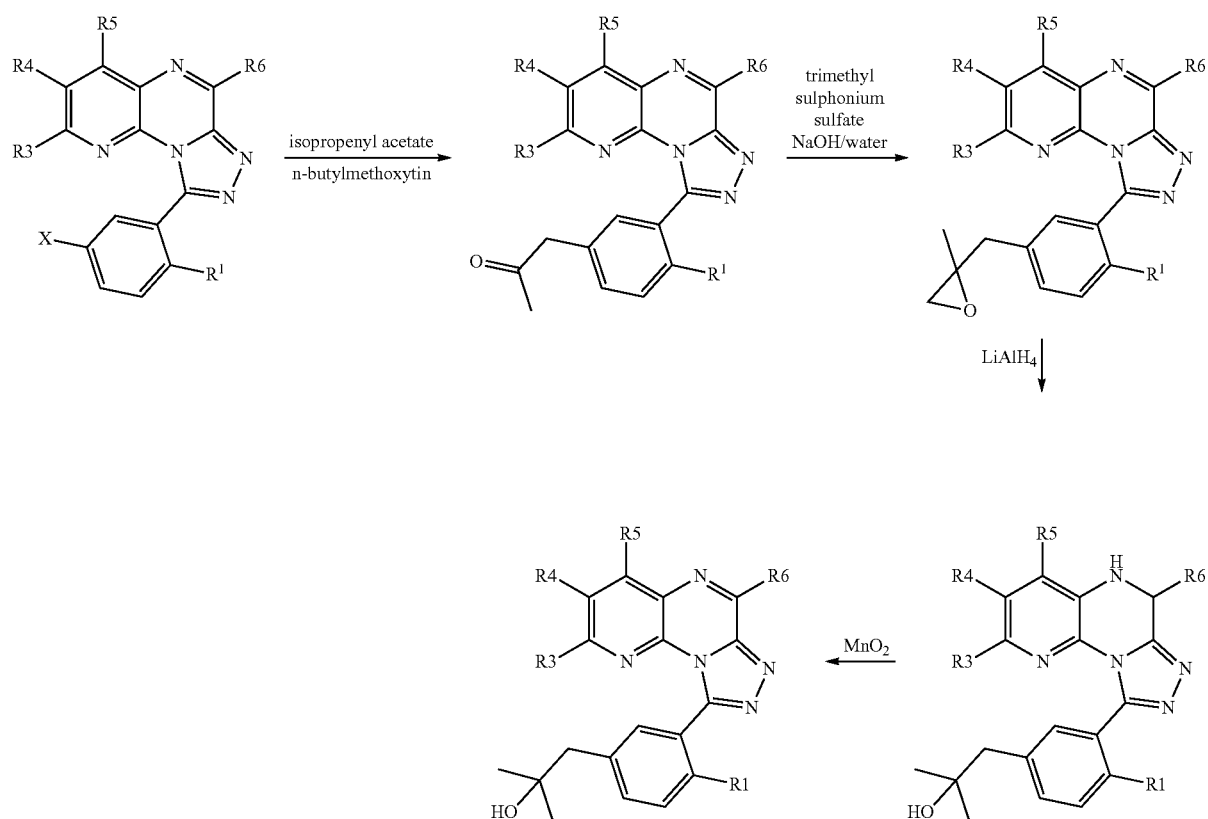
In analogy, the omologated derivatives Examples 80, 81 were obtained performing the first step as described in Scheme 9a.

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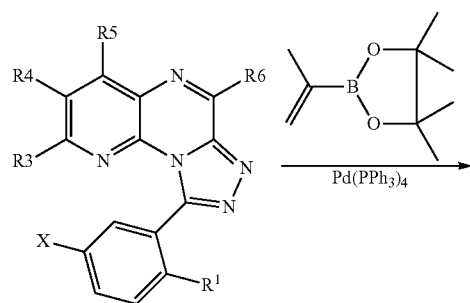
-continued



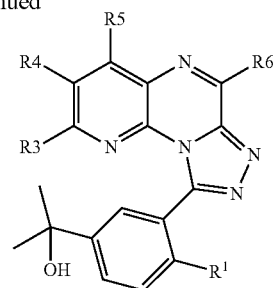
Scheme 9



Scheme 10



-continued



Further examples of the present invention were prepared as described in Scheme 10: in a first step the appropriate double

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bond is installed by Suzuki coupling with suitable boronic acids or esters (such as for example 2-isopropenyl-dioxaborolane, Scheme 10). In a second step, the hydration of the double bond (HCl/dioxane) allowed to introduce hydroxylic function.

Example 103,103b,103c were prepared following the above described procedure.

The compounds according to the invention are advantageously also obtainable using the methods described in the examples that follow, which may also be combined for this purpose with methods known to the skilled man from the literature.

As already mentioned, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly as inhibitors of phosphodiesterase 2 and/or 10.

BIOLOGICAL EXAMPLES

In-vitro Effect:

The in-vitro effect of the active compounds of the invention can be shown with the following biological assays.

a) Radioactive PDE2 Assay Protocol:

For all experiments the Phosphodiesterase [^3H]cAMP SPA Enzyme Assay (TRKQ7090, GE Healthcare Europe GmbH) were used. The enzymatic activity of the PDE2 and the inhibitory potency of compounds was measured by the conversion of [^3H]cAMP to [^3H]AMP. [^3H]AMP associate to the scintillator soaked yttrium-silicate beads resulting in an increase in scintillation events. Compounds that inhibit the respective enzymes decrease the generation of [^3H]AMP and accordingly the number of counts detected.

SF9 lysate containing PDE2A is incubated at room temperature for 1 h with [^3H]cAMP and the reaction is terminated by addition of SPA beads in 18 mM zinc sulphate. The [^3H]AMP bound to SPA beads is determined after at least 3 hours of sedimentation of the beads, the signal is recorded using the TopCount with a recording time of 3 min/well.

PDE 2A protein is expressed upon baculovirus infection in SF9 cells. The cells have been incubated upon infection for ~3 days and protein production was confirmed by Western Blot. The cells were collected by centrifugation and the pellet frozen in liquid nitrogen before it was resuspended in PBS containing 1% Triton X-100 and protease inhibitors. After 45 min incubation on ice, the cell debris was removed by centrifugation (13.000 rpm, 30 min).

The assay conditions were as follows:

total assay volume:	40 μl
protein amount:	5 ng
protein concentration:	500 pg/ μl
substrate concentration:	20 nM; ~1.08 mCi/l
incubation time:	60 min

The buffer used for above described assay buffer was:

50 mM Tris/HCl, pH 7.4
8.3 mM MgCl_2
1.7 mM EGTA
0.1% (w/v) BSA
0.05% (v/v) Tween 20

In detail the protocol is as follows:

Into a 384 well plate (OptiPlate, white), the following components are pipetted (either manually or using automated pipetting devices):

72

20 μl test-compound solution (test compound diluted in assay buffer at twofold the desired concentration)

+10 μl PDE 2A preparation (enzyme diluted in assay buffer to a concentration of 0.5 ng/ μl protein)

5 +10 μl [^3H]cAMP (diluted in assay buffer to a concentration of 80 nM cAMP)

Controls included into each experiment:

positive control: no inhibitor, DMSO at the concentration as used in the compound dilutions

10 negative control: no PDE 2 (SF9 lysate instead of SF9/PDE 2A lysate)

Calculation of % Inhibition:

15 The activity of the positive control (minus the negative control=background) is set to 100% and activity in the presence of compound is expressed relative to these 100%.

Calculation of IC₅₀:

20 IC₅₀ are calculated with GraphPadPrism or other suited software setting the positive control as 100 and the negative control as 0. For calculation of IC₅₀ usually 11 dilutions of the test compound are selected.

b) Radioactive PDE10 Assay Protocol:

For assessing activity of compounds on PDE10 inhibition, the following modifications of the protocol described above are applied:

25 protein amount: 3 ng

protein concentration: 75 $\mu\text{g}/\mu\text{l}$

In detail the protocol is as follows:

30 Into a 384 well plate (OptiPlate, white), the following components are pipetted (either manually or using automated pipetting devices):

20 μl test-compound solution (test compound diluted in assay buffer at twofold the desired concentration)

+10 μl PDE 10A preparation (enzyme diluted in assay buffer to a concentration of 0.3 ng/ μl protein)

35 +10 μl cAMP tracer (diluted in assay buffer to a concentration of 80 nM cAMP, specific activity ~4 mCi/I)

After addition of all 3 components the plates are shortly spun and incubated at room temperature for 60 min. The reaction is stopped by the addition of 20 μl Yttrium SPA PDE Beads containing 18 mM zinc sulphate in water

After at least 3 hours sedimentation of the beads, the signal is recorded using the TopCount with a recording time of 3 min/well.

45 PDE 10A protein is expressed upon baculovirus infection in SF9 cells. The cells have been incubated upon infection for ~3 days and protein production was confirmed by Western Blot. The cells were collected by centrifugation and the pellet frozen in liquid nitrogen before it was resuspended in PBS containing 1% Triton X-100 and protease inhibitors. After 45 min incubation on ice, the cell debris was removed by centrifugation (13.000 rpm, 30 min).

In the following table the results of the above described experiments are listed.

TABLE 3

Activity of the examples (Ex) compiled in the experimental part, based on above described assays (cAMPA SPA radioactive).

Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]
1	0.016	0.421
2	0.004	0.040
3	0.155	0.411
4	0.138	0.441
13	0.053	2.190
14	0.202	3.580

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TABLE 3-continued

Activity of the examples (Ex) compiled in the experimental part, based on above described assays (cAMPA SPA radioactive).		
Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]
15	0.040	>10
16	0.058	1.876
17	0.098	5.72
18	0.071	3.01
19	0.146	3.01
20	0.028	2.76
21	0.070	2.82
22	0.115	>5
23	0.071	5.10
24	0.138	6.69
25	0.055	3.26
26	0.116	1.38
27	0.004	0.97
28	0.009	>10
29	0.017	2.38
30	0.027	3.92
31	0.007	1.90
32	0.003	1.76
33	0.004	2.50
34	0.009	1.89
35	0.009	1.30
36	0.219	0.85
37	0.171	3.08
38	0.417	1.96
39	0.914	2.10
40	0.080	3.47

Another, non radioactive, in-vitro assay was performed as follows

c) Phosphodiesterase (PDE) 2A and 10 Assay with Fluorescent Substrate

Assay Principle:

The PDE reaction cleaves cAMP to AMP. The IMAP system (Molecular Device) using fluorescence polarization (FP) as detection principle was used to measure enzyme activity. A fluorescent labeled cAMP was used as substrate for the reaction, generating a labeled AMP. The fluorescent AMP binds specifically to the large M(III)-based nano-particles which reduces the rotational speed of the substrate and thus increases its polarization.

Detailed Method:

The inhibition of PDE 2A or 10 enzyme activity was assessed using IMAP-Phosphodiesterase-cAMP fluorescence labeled substrate (Molecular Devices, Order No. R7506), IMAP TR-FRET screening express (Molecular Devices, Order No. R8160, the TR-FRET component will not be used) and PDE 2A or PDE10 protein expressed upon baculovirus infection in SF9 cells. The cells were incubated after infection for ~3 days and protein production was confirmed by Western Blot. The cells were collected by centrifugation and the pellet frozen in liquid nitrogen before it was resuspended in PBS containing 1% Triton X-100 and protease inhibitors. After 45 min incubation on ice, the cell debris was removed by centrifugation (13.000 rpm, 30 min). Since SF 9 cells do not express cAMP hydrolyzing enzymes to a high extent, no further purification of the protein was needed.

All reactions were performed in 384 well plates, Perkin Elmer black optiplates and IMAP reaction buffer with 0.1% Tween20 (kit component)

Compounds were serial diluted in DMSO. With an intermediate dilution step with reaction buffer DMSO concentration was reduced to achieve 1% DMSO in the assay reaction. Setup of the assay started with 10 μl enzyme (~10 ng/well, depending on prep. batch), 5 μl compound, reaction was started by addition of 5 μl labeled cAMP (30 nM, final con-

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centration), immediately mixed for 15 seconds on a Eppendorf mixmate (2000 rpm) followed by an incubation at room temperature for 90 minutes in the dark. Reaction is stopped by adding of 60 μl binding buffer for FP/cAMP (kit component). After at least 90 min of further incubation (room temperature, dark) the assay was measured at 485 nm excitation/525 nm emission in an Envision multilabel reader (PerkinElmer).

Each assay plate contained wells with vehicle controls (1% DMSO) for the measurement of non-inhibited reaction (=100% control) and wells without enzyme as 0% controls.

The analysis of the data was performed by calculation of the percentage of inhibition in the presence of test compound compared to the vehicle control samples (100% control, no inhibition) and a low control (0% control, no enzyme). IC50 values are calculated with Assay Explorer or other suited software based on curve fitting of results of at least 8 different compound concentrations. The compound concentrations may vary according to the needed range, but typically cover the range between 10 μM and 0.1 pM.

TABLE 3a

Activity of the examples (Ex) compiled in the experimental part, based on above described assays (IMAP fluorescent).		
Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]
1	0.041	0.355
2	0.003	0.033
4	0.120	0.256
5	0.003	0.005
6	0.003	0.010
7	0.003	0.016
8	0.002	0.008
9	0.001	0.015
10	0.229	0.254
11	0.059	0.123
12	0.009	0.044
12a	0.036	0.170
13	0.095	6.363
15	0.112	1.118
16	0.098	8.700
17	0.162	10.200
18	0.090	8.418
20	0.077	8.162
21	0.022	7.047
22	0.207	9.317
23	0.216	9.193
25	0.038	7.333
27	0.018	0.958
28	0.020	0.299
29	0.037	5.097
30	0.020	2.573
31	0.008	2.897
32	0.026	6.703
32a	0.006	7.390
33	0.005	3.417
34	0.017	2.143
35	0.017	1.477
35a	0.003	0.822
40	0.077	8.707
41	0.050	2.770
42	0.035	2.520
43	0.057	3.015
43a	0.109	4.510
44	0.156	6.037
45	0.005	1.488
46	0.050	1.035
47	0.008	0.852
48	0.008	1.520
49	0.033	3.760
50	0.194	7.120
51	0.009	2.150
52	0.011	1.195
53	0.140	2.830
54	0.058	0.798

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TABLE 3a-continued

Activity of the examples (Ex) compiled in the experimental part, based on above described assays (IMAP fluorescent).		
Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]
55	0.080	5.298
55a	0.033	2.435
56	0.002	0.061
56a	0.008	0.061
56b	0.001	0.066
57	0.006	0.045
57a	0.012	0.167
57b	0.003	0.091
58	0.143	0.663
58a	0.054	0.713
58b	0.045	0.663
58c	0.037	0.241
59	0.008	0.936
60	0.019	0.285
61	0.004	0.534
62	0.011	1.300
63	0.060	1.710
64	0.045	3.870
65	0.214	3.545
66	0.003	0.674
67	0.175	3.905
68	0.002	1.007
69	0.001	0.891
70	0.163	8.620
71	0.109	2.080
72	0.032	2.865
73	0.189	10.000
74	0.131	2.340
75	0.012	2.403
76	0.021	1.105
77	0.004	1.400
78	0.010	2.845
79	0.144	0.305
80	0.010	5.405
81	0.007	5.384
82	0.199	5.615
83	0.004	8.815
84	0.006	0.565
85	0.006	4.325
86	0.434	5.750
87	0.074	2.594
88	0.001	0.302
89	0.018	0.187
90	0.103	0.485
91	0.001	0.077
92	0.002	0.553
93	0.086	6.107
94	0.001	2.719
95	0.005	1.369
96	0.043	5.945
96a	0.199	10.000
96b	0.087	10.000
96c	0.591	7.460
97	0.004	2.142
97a	0.004	5.945
97b	0.004	0.891
98	0.139	1.560
99	0.125	1.510
100	0.017	3.856
101	0.047	1.125
102	0.103	2.265
103	0.003	1.007
103b	0.100	10.000
103c	0.622	7980
104	0.036	7.715
104a	0.040	3.229
104b	0.030	9.765
105	0.023	1.540
105a	0.104	3.630
105b	0.038	3.410
106	0.160	1.940
106a	0.429	1.410
106b	0.050	2.500
107	0.007	0.022

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TABLE 3a-continued

Activity of the examples (Ex) compiled in the experimental part, based on above described assays (IMAP fluorescent).		
Ex.	PDE2 IC ₅₀ [μM]	PDE10 IC ₅₀ [μM]
111	0.022	3.980
108a	0.011	0.548
108b	0.059	0.594
108c	0.024	0.262
108d	0.046	0.630
109a	0.014	1.670
109b	0.009	1.090
109c	0.009	1.360
109d	0.004	1.830
110b	0.388	>10
110d	0.467	7.600
111a	0.065	1.830
111b	0.011	2.130
112	0.018	7.000
112a	0.025	2.600
112b	0.068	2.500
113	0.0002	3.190
114	0.022	10.000
114a	0.009	10.000
114b	0.011	10.000
115	0.039	10.000
115a	0.082	10.000
115b	0.045	10.000

In-vivo Effect:

Animal Experiments and Sample Analysis (CSF):

Test compounds were administered to animals (rat) different routes at doses of 10.0 or 5 μmol/kg, (both oral and intravenous). After compound administration, the animals were sacrificed in a CO₂ chamber and CSF samples were carefully collected by puncture of the cisterna magna. Immediately after CSF sampling, blood was taken by heart puncture and brains were dissected out. Blood was collected in EDTA-coated microvettes and plasma was prepared by centrifugation. Concentration of the test compounds in plasma, CSF or brain homogenate was determined using HPLC-MS-MS.

TABLE 4

Plasma, brain and CSF concentration						
Ex.	Time(*) (h)	conc plasma (nmol/L)	conc brain (nmol/L)	c(brain)/ c(plasma)	conc CSF (nmol/L)	c(CSF)/ c(plasma)
44	0.5	2187	670	0.31	228	0.10
34	0.5	223	146	0.7	19	0.09
18	0.5	1225	351	0.3	163	0.13
20	0.5	338	272	0.82	37	0.11
45	2	801	183	0.20	25	0.03
64	2	783	254	0.5	37	0.06
76	2	463	218	0.5	18	0.04
75	2	1130	383	0.34	31	0.03
70	2	2377	695	0.29	276	0.12
47	2	622	441	0.7	22	0.04
49	2	239	47	0.2	13	0.06

(*)Time between administration and CSF sampling

For the skilled in the art it is evident from the experimental results shown above that the compounds of the present invention are not only very potent phosphodiesterase 2 and/or 10 inhibitors but also reach high CSF concentrations and adequate CSF to plasma ratios.

Metabolic Stability

The metabolic stability of the compounds according to the invention has been investigated as follows:

The metabolic degradation of the test compound was assayed at 37° C. with pooled liver microsomes from various species. The final incubation volume of 100 µl per time point contains TRIS buffer pH 7.6 at room temperature (0.1 M), magnesium chloride (5 mM), microsomal protein (1 mg/mL for human and dog, 0.5 mg/mL for other species) and the test compound at a final concentration of 1 µM. Following a short preincubation period at 37° C., the reactions were initiated by addition of betanicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM), and terminated by transferring an aliquot into solvent after different time points. After centrifugation (10000 g, 5 min), an aliquot of the supernatant was assayed by LC₁₀ MS/MS for the amount of parent compound. The half-life was determined by the slope of the semi-logarithmic plot of the concentration-time profile.

TABLE 4

Stability of compounds of the present invention in human liver microsomes.	
Ex.	Half-life - t _{1/2} [min]
1	130
5	43
6	66
9	41
12	63
13	130
17	130
18	130
20	130
21	130
30	130
32	130
32a	36
34	130
35	130
35a	130
42	130
43	130
44	130
45	130
46	130
47	130
48	130
49	130
50	130
51	130
52	130
54	130
55	130
55a	130
56	120
56a	110
56b	62
57	130
57a	130
57b	93
58	130
58a	130
58b	130
58c	130
59	49
61	65
62	130
63	130
64	130
66	57
67	130
68	39
69	53
70	130
71	130

TABLE 4-continued

Stability of compounds of the present invention in human liver microsomes.	
Ex.	Half-life - t _{1/2} [min]
72	130
73	130
75	130
76	130
77	90
78	79
80	83
81	26
82	130
83	100
84	39
85	130
87	130
88	53
89	130
91	28
92	23
93	130
94	38
96	110
97	51
99	130
100	12
101	22
102	130
104	130
104a	130
104b	130

hERG (Human Ether-à-go-go-Related Gene)-Channel Assay
hERG channel inhibition of compounds of the present invention has been investigated as follows:

HEK (human embryonic kidney) 293 cells were stably transfected with hERG cDNA.

Cells were superfused with a bath solution containing (mM): NaCl (137), KCl (4.0), MgCl₂ (1.0), CaCl₂ (1.8), Glucose (10), HEPES (10), pH 7.4 with NaOH. Patch pipettes were made from borosilicate glass tubing using a horizontal puller and filled with pipette solution containing (mM): K-aspartate (130), MgCl₂ (5.0), EGTA (5.0), K₂ATP (4.0), HEPES (10.0), pH 7.2 with KOH. Resistance of the micro-electrodes was in the range between 2 and 5 MΩ.

Stimulation and recording:

Membrane currents were recorded using an EPC-10 patch clamp amplifier and PatchMaster software. hERG-mediated membrane currents were recorded at 35° C., using the whole-cell configuration of the patch-clamp technique. Transfected HEK293 cells were clamped at a holding potential of -60 mV and hERG-mediated inactivating tail currents were elicited using a pulse pattern with fixed amplitudes (activation/inactivation: 40 mV for 2000 ms; recovery: 120 mV for 2 ms; ramp to 40 mV in 2 ms; inactivating tail current: 40 mV for 50 ms) repeated at 15 s intervals. During each inter-pulse interval 4 pulses scaled down by a factor of 0.2 were recorded for a P/n leak subtraction procedure. Rs compensation was employed up to a level that safely allowed recording devoid of ringing.

Compound preparation and application:

The different concentrations of the test compound were applied sequentially on each of the different cells investigated. A steady state level of baseline current was measured for at least 6 sweeps prior to the application of the first test compound concentration.

The test compound was dissolved in DMSO to yield a master stock solution which was diluted further in DMSO to stock solutions needed for the lower concentrations. Final

dilutions in extracellular buffer were prepared freshly from these stocks by a 1:1000 dilution step each before starting the experiments.

Data analysis and IC₅₀ determination:

Peak current amplitudes were measured 3 ms after the ramp to +40 mV. For baseline and each concentration the peak currents of the three last sweeps before application of the next concentration were averaged. Residual currents (I/I₀) were calculated for each cell as the fraction of actual average peak current and average baseline peak current.

The logistic concentration-response curve of the following form was fitted to the residual current data using a genetic algorithm:

$$I/I_0 = 1 - 1 / (1 + (C/IC_{50})^{*p})$$

C: actual concentration of compound (in μ M)

IC₅₀: half-inhibitory concentration (in μ M)

p: Hill slope

TABLE 4

hERG channel inhibition of compounds of the present invention.	
Ex.	hERG IC ₅₀ [μ M]
13	>10
18	>10
20	>10
21	>10
27	>10
28	>10
32	>10
32a	>10
34	>10
35a	>10
45	>10
47	>10
48	>10
49	>10
55	>10
64	>10
66	>10
68	8.3
75	>10
76	>10
80	>10
82	>10
83	>10
84	6.3
85	>10
87	>10
88	>10
93	>10

In view of their ability to inhibit the activity of phosphodiesterase 2 and/or 10 activity, their CSF values and their metabolic stability and their low inhibition of the hERG channel, the compounds of general formula I according to the invention, including the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the hydrates thereof, the solvates and the physiologically acceptable salts thereof, are suitable for the treatment and/or preventative treatment of all those diseases or conditions which can be influenced by inhibition of PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction. Therefore, compounds according to the invention, including the physiologically acceptable salts thereof, are particularly suitable for the prevention or treatment of diseases, particularly (1) disorders comprising the symptom of cognitive deficiency; (2) organic, including symptomatic, mental disorders, dementia; (3) mental retardation; (4) mood [affective] disorders; (5) neurotic, stress-related and somatoform disorders including anxiety disorders; (6) behavioural and emotional disorders with onset

usually occurring in childhood and adolescence, attention deficit hyperactivity syndrome (ADHD) and Autism spectrum disorders; (7) disorders of psychological development, developmental disorders of scholastic skills; (8) schizophrenia and other psychotic disorders; (9) disorders of adult personality and behaviour; (10) mental and behavioural disorders due to psychoactive substance use; (11) extrapyramidal and movement disorders; (12) episodic and paroxysmal disorders, epilepsy; (13) Systemic atrophies primarily affecting the central nervous system, ataxia; (14) Behavioural syndromes associated with physiological disturbances and physical factors; (15) sexual dysfunction comprising excessive sexual drive; (16) factitious disorders.

In addition, the compounds according to the invention can be used for the treatment, amelioration and/or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

In addition, the compounds according to the invention can be used for the treatment amelioration and/or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis. In addition, the compounds of the present invention can be used for the treatment of Alzheimer's disease.

In addition compounds according to the invention can be used for the treatment of pain disorders including but not limited to inflammatory, neuropathic and osteoarthritic pain.

In addition, the compounds according to the invention can be used for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

Preferably the compounds according to the invention are suitable for the treatment of Alzheimer's Disease and for the treatment schizophrenia.

More preferably the compounds according to the invention are suitable for symptomatic treatment of Alzheimer's Disease and for the treatment of cognitive impairment associated with schizophrenia.

In particular the compounds according to the invention are suitable for symptomatic treatment of prodromal and mild-to-moderate Alzheimer's Disease and for the treatment of cognitive impairment associated with schizophrenia.

In a further aspect of the present invention the present invention relates to methods for the treatment or prevention of above mentioned diseases and conditions, which method comprises the administration of an effective amount of a compound of general formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the hydrates thereof, the solvates and the physiologically acceptable salts thereof, to a human being.

The dose range of the compounds of general formula I applicable per day is usually from 0.1 to 1000 mg, preferably from 1 to 500 mg by oral route, in each case administered 1 to 4 times a day.

Each dosage unit may conveniently contain from 0.1 to 500 mg, preferably 1 to 100 mg.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

Suitable preparations for administering the compounds of formula I, including the physiologically acceptable salts thereof, will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives, powders, etc. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 95 wt.-%, preferably 5.0 to 90 wt.-% of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula I with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers.

For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, citric acid, tartaric acid, water, polyvinylpyrrolidone, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof.

The compounds according to the invention may also be used in conjunction with other active substances, particularly for the treatment and/or prevention of the diseases and conditions mentioned above. Other active substances which are suitable for such combinations include, for example, BACE inhibitors; amyloid aggregation inhibitors (e.g. ELND-005); directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants (e.g. vitamin E or ginkgolide); anti-inflammatory substances (e.g. Cox inhibitors, NSAIDs additionally or exclusively having Abeta lowering properties); HMG-CoA reductase inhibitors (statins); acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, tacrine, galantamine); NMDA receptor antagonists (e.g. memantine); AMPA receptor agonists; AMPA receptor positive modulators, AMPAkinase, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone (e.g., ibutamoren mesylate and capromorelin); CB-1 receptor antagonists or inverse agonists; antibiotics (e.g., minocycline or rifampicin); PDE2, PDE4, PDE5, PDE9, PDE10 inhibitors, GABAA receptor inverse agonists, GABAA receptor antagonists, nicotinic receptor agonists or partial agonists or positive modulators, alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators, alpha7 nicotinic receptor agonists or partial agonists or positive modulators; histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, alpha2-adrenoreceptor antagonists, calcium antagonists, muscarinic receptor M1 agonists or partial agonists or positive modulators, muscarinic receptor M2 antagonists, muscarinic receptor M4 antagonists, metabotropic glutamate-receptor 5 positive modulators, glycine transporter 1 inhibitors, antidepressants, such as citalopram, fluoxetine, paroxetine, sertraline and trazodone; anxiolytics, such as lorazepam and

oxazepam; antipsychotics, such as aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced. The compounds according to the invention may also be used in combination with immunotherapies (e.g., active immunisation with Abeta or parts thereof or passive immunisation with humanised anti-Abeta antibodies or nanobodies) for the treatment of the above-mentioned diseases and conditions.

The dosage for the combination partners mentioned above is usefully 1/5 of the lowest dose normally recommended up to 1/1 of the normally recommended dose.

Therefore, in another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt thereof combined with at least one of the active substances described above as a combination partner, for preparing a pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions which can be affected by inhibitors of phosphodiesterase 2 and/or 10. These are preferably pathologies related to PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction, particularly one of the diseases or conditions listed above, most particularly prodromal and mild-to-moderate Alzheimer's Disease and cognitive impairment associated with schizophrenia.

The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; while if they are used at staggered times the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

Consequently, in another aspect, this invention relates to a pharmaceutical composition which comprises a compound according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally together with one or more inert carriers and/or diluents.

The compound according to the invention, or a physiologically acceptable salt thereof, and the additional active substance to be combined therewith may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as a so-called kit-of-parts.

EXAMPLES

The following examples are intended to illustrate the invention, without restricting its scope.

Chemical Manufacture

Abbreviations

ACN acetonitrile

APCI Atmospheric pressure chemical ionization

d day

Cy cyclohexane

DCM dichloromethane

DIPEA diisopropylethylamine

DMF dimethylformamide

DMA dimethylacetamide

ESI electrospray ionization (in MS)

EtOAc ethylacetate

EtOH ethanol

Ex. example

h hour(s)
 HATU O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate
 HPLC high performance liquid chromatography
 HPLC-MS coupled high performance liquid chromatography-mass spectrometry
 M molar (mol/L)
 MeOH methanol
 min minute(s)
 MS mass spectrometry
 NMP 1-methyl-2-pyrrolidinone
 rt room temperature
 R_t retention time (in HPLC)
 TBTU O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
 TEA triethylamine
 TFA trifluoroacetic acid
 THF tetrahydrofuran
 TLC thin-layer chromatography
 UPLC-MS ultra performance liquid chromatography-mass spectrometry
 Methods:
 UPLC-MS methods:
 Method 1

Instrument: LC/MS Waters Acquity UPLC System DAD, SQD single quadrupole; column: HSS C18 1.8 μ m 2.1 \times 50 mm, Temp 35° C.; mobile phase: A=H₂O 90%+10% CH₃CN+CF₃COOH 0.1%, B=CH₃CN 90%+H₂O 10%; gradient: 0.0 min 0% B \rightarrow 1.20 min 100% B \rightarrow 1.45 min 100% B \rightarrow 1.55 min 0% B \rightarrow 1.75 min 0% B; flow rate: 0.70 mL/min; detection: UV 254 nm; detection: SQD, single quadrupole; ion source: ES+/ES-; scan range: 90-900 amu.

Method 2

Instrument: LC/MS Waters Acquity UPLC System DAD, SQD single quadrupole; column: BEH C18 1.7 μ m 2.1 \times 50 mm, Temp 35° C.; mobile phase: A=H₂O 90%+10% CH₃CN+NH₄COOH 5 mmol, B=CH₃CN 90%+H₂O 10%; gradient: 0.0 min 0% B \rightarrow 1.20 min 100% B \rightarrow 1.45 min 100% B \rightarrow 1.55 min 0% B \rightarrow 1.75 min 0% B; flow rate: 0.70 mL/min; detection: UV 254 nm; detection: SQD, single quadrupole; ion source: ES+/ES-; scan range: 90-900 amu.

Method 3

Instrument: LC/MS Waters Acquity UPLC System DAD, ELSD detector, SQD single quadrupole; column: HSS C18 1.8 μ m 2.1 \times 50 mm, Temp 35° C.; mobile phase: A=H₂O 90%+10% CH₃CN+CF₃COOH 0.1%, B=CH₃CN 90%+H₂O 10%; gradient: 0.0 min 0% B \rightarrow 2.40 min 100% B \rightarrow 2.70 min 100% B \rightarrow 2.80 min 0% B \rightarrow 3.00 min 0% B; flow rate: 0.70 mL/min; detection: UV 254 nm; detection: ELSD detector; detection: SQD, single quadrupole; ion source: ES+/ES-; scan range: 90-900 amu.

Method 4

Instrument: LC/MS Waters Acquity UPLC System DAD, ELSD detector, SQD single quadrupole; column: HSS C18 1.8 μ m 2.1 \times 50 mm, Temp 35° C.; mobile phase: A=H₂O 90%+10% CH₃CN+NH₄COOH 5 mmol, B=CH₃CN 90%+H₂O 10%; gradient: 0.0 min 0% B \rightarrow 2.40 min 100% B \rightarrow 2.70 min 100% B \rightarrow 2.80 min 0% B \rightarrow 3.00 min 0% B; flow rate: 0.70 mL/min; detection: UV 254 nm; detection: ELSD detector; detection: SQD, single quadrupole; ion source: ES+/ES-; scan range: 90-900 amu.

HPLC-MS Methods:

Method 5

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column: Synergi Hydro-RP80A, 4 μ m, 4.60 \times 100 mm; eluent A: 90% water+10% ACN+ammonium formate 10 mM; eluent B=ACN 90%+10% H₂O+

NH₄COOH 10 mM; gradient: A (100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV Detection: 254 nm; Ion source: APCI.

Method 6

Instrument: LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQ Fleet Ion Trap; column:

Simmetry Shield RPB, 5 μ m, 4.6 \times 150 mm; eluent A: 90% water+10% ACN+HCOOH 0.1%; eluent B=ACN 90%+10% H₂O+HCOOH 0.1%; gradient: 0.0 min 5% B \rightarrow 1.5 min 5% B \rightarrow 11.5 min 95% B \rightarrow 13.0 min 95% B \rightarrow 13.3 min 5% B \rightarrow 15.0 min 5% B; flow rate: 1.0 mL/min; UV Detection: 254 nm; Detection: Finnigan Fleet, Ion Trap; ion source: ES+; scan range: 100-900 amu.

Method 7

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column: Synergi Hydro-RP8, 4 μ m, 4.60 \times 100 mm; eluent A: 90% water+10% ACN+ammonium formate 10 mM; eluent B=ACN 90%+10% H₂O+NH₄COOH 10 mM; gradient: 0.0 min 30% B \rightarrow 1.50 min 50% B \rightarrow 8.50 min 100% B \rightarrow 13.50 min 100% B \rightarrow 14.00 min 30% B \rightarrow 15.00 min 30% B; flow rate: 0.85 mL/min; UV Detection: 254 nm; Ion source: ES+.

Method 8

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column: Synergi Hydro-RP100A, 2.5 μ m, 3 \times 50 mm; eluent A: 90% water+10% ACN+ammonium formate 10 mM; eluent B=ACN 90%+10% H₂O+NH₄COOH 10 mM; gradient: A (100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 0.7 mL/min; UV Detection: 254 nm; Ion source: APCI.

Method 9

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column: Synergi Hydro-RP100A, 2.5 μ m, 3 \times 50 mm; eluent A: 90% water+10% ACN+NH₄COOH 5 mM; eluent B=ACN 90%+10% H₂O; gradient: A (100), then to B (100) in 4 min for 1.3 min; flow rate: 1.2 mL/min; UV Detection: 254 nm; Ion source: APCI.

Method 13

Instrument: LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQ Fleet Ion Trap; column: Xselect CSH, 2.5 μ m, 4.6 \times 50 mm; eluent A: 90% water+10% ACN+HCOOH 0.1%; eluent B=ACN 90%+10% H₂O+HCOOH 0.1%; gradient: A (100), then to B (100) in 4 min for 1.3 min; then to A(100) in 1.6 min. flow rate: 1.4 mL/min; UV Detection: 254 nm; Ion source: ESI.

Method 16

Instrument: LC/MS Waters Alliance 2695 HPLC System DAD, Quattro Micro Triple quadrupole; Column: Atlantis dC18 5 μ m 4.6 \times 50 mm, Temp 35° C.; Mobile phase: A=H₂O 90%+10% CH₃CN+CF₃COOH 0.05%; B=CH₃CN 90%+10% H₂O; flow rate: 1.3 mL/min; UV Detection: 254 nm; Ion source: ESI.

Gradient:

Time in min	% A	% B
0.00	100	0
0.70	100	0
4.5	0	100
5.80	0	100
6.00	100	0

Method 17

Instrument: LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQ Fleet Ion Trap; column: Xselect CSH, 2.5 μ m, 4.6 \times 50 mm; eluent A: 90% water+10% ACN+HCOOH 0.1%;

85

eluent B=ACN 90%+10% H₂O+HCOOH 0.1%; flow rate: 1.4 mL/min; UV Detection: 254 nm; Ion source: ESI.
Gradient:

Time in min:	% A	% B
0.00	100	0
1.00	100	0
8.50	0	100
10.0	0	100
10.2	100	0
11.0	100	0

GC-MS Methods:

Method 10 (3A.2)

Instrument: GC/MS Thermo Scientific TRACE GC ULTRA, DSQ II MS single quadrupole; column: Agilent DB-5MS, 25m×0.25 mmol×0.25 μm; carrier gas: Helium, 1 mL/min constant flow; oven program: 50° C., to 100° C. in 10° C./min, to 200° C. in 20° C./min, to 320° C. in 30° C./min (hold 10 min); detection: DSQ II MS single quadrupole; ion source: EI; scan range: 50-450 amu.

Preparative HPLC Methods:

Method 11:

Instrument: Waters Autopurification HPLC/MS System; column: Sunfire C18, ODB 5.0 μm, 19×100 mm. MS Zq single quadrupole; eluent A: 90% water+0.05% TFA; eluent B=ACN gradient: 0.0 min 20% B→6.5 min 60% B→7.0 min 95% B→8.5 min 20% B flow rate: 40 mL/min; UV Detection: 254 nm; Ion source: ES+.

Method 12:

Instrument: Waters Autopurification HPLC/MS System; column: Sunfire C18, ODB 5.0 μm, 19×100 mm. MS Zq single quadrupole; eluent A: 90% water+0.05% TFA; eluent B=ACN gradient: 0.0 min 50% B→6.5 min 90% B→7.0 min 95% B→8.5 min 50% B flow rate: 40 mL/min; UV Detection: 254 nm; Ion source: ES+.

Method 14:

Instrument: Waters Autopurification HPLC/MS System; column: Xbridge, C18 5 μm, 19×100 mm. MS Zq single quadrupole; eluent A: 90% water+NH₄COOH 5 mM, eluent B=ACN gradient: 0.0 min 40% B→6.5 min 80% B→7.0 min 95% B→8.0 min 95% B→8.5 min 40% B flow rate: 40 mL/min; UV Detection: 254 nm; Ion source: ES+.

Method 15

Instrument: Waters Autopurification HPLC/MS System; column: Xbridge, C18 5 μm, 19×100 mm. MS Zq single quadrupole; eluent A: 90% water+NH₄COOH 5 mM, eluent B=ACN gradient: 0.0 min 30% B→6.5 min 80% B→6.50 min 70% B→8.0 min 95% B→8.5 min 30% B flow rate: 40 mL/min; UV Detection: 254 nm; Ion source: ES+.

Chiral HPLC Methods:

Instrument: HPLC Agilent 1100 (DAD equipped; UV Detection: 230 nm); flow rate: 15 mL/min; column temperature: 25° C.

Method C1

column: Daicel Chiralpack AS-H; eluent: Hexane:EtOH=70:30

Method C1a

column: Daicel Chiralpack AS-H; eluent: Hexane:EtOH=80:20

Method C2

column: Daicel Chiralpack AD-H; eluent: Hexane:Isopropanol=70:30

Method C2a

column: Daicel Chiralpack AD-H; eluent: Hexane:Isopropanol=75:25

86

Method C2b

column: Daicel Chiralpack AD-H; eluent: Hexane:Isopropanol=80:20

Method C2c

column: Daicel Chiralpack AD-H; eluent: Hexane:Isopropanol=60:40

Method C3

column: Daicel Chiralcel OJ-H; eluent: Hexane:EtOH=80:20

The most suitable purification techniques applied for the purification of compounds of the present invention are direct phase silica gel flash chromatography and reverse phase chromatography or preparative HPLC,

General Comment Concerning the Presentation of the Structures

Compounds with stereogenic centre(s): The structures depicted in the experimental section will not necessarily show all the stereochemical possibilities of the compounds but only one.

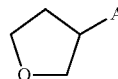
The structural presentation of the compounds in the experimental section will show a stereochemical bond only in case where the absolute stereochemistry is known.

The structural presentation of the compounds in the experimental section with unknown absolute stereochemistry will show a planar bond plus an additional comment that indicates if the described compound is a racemic mixture, a single stereoisomer and where applicable the relative stereochemistry.

Two examples are given below.

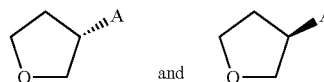
Example 1

the Presented Chemical Structure is Depicted as

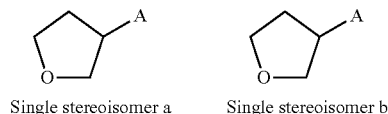


Racemic Mixture

The added term racemic mixture points to the two stereochemical options and thus the manufactured compounds is a mixture of:



When racemic mixtures of above depicted structures are separated, the single stereoisomers are depicted as:



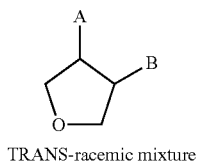
The added term 'single stereoisomer' indicates that the absolute configuration is unknown.

87

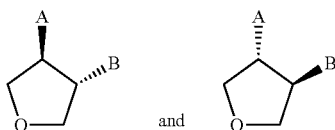
Single stereoisomer a is assigned to the first eluting isomer in chiral HPLC, single stereoisomer b is assigned to the second eluting isomer in chiral HPLC.

Example 2

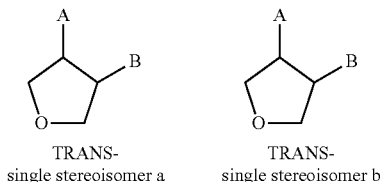
the Presented Chemical Structure is Depicted as



The added term 'TRANS-racemic mixture' points to the two stereochemical options and thus the manufactured compounds is a mixture of:



The same principles applies to 'CIS-racemic mixture'. When racemic mixtures of above depicted structures are separated, the single stereoisomers are depicted as:

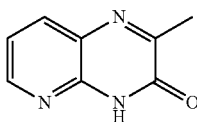


The added term 'TRANS-single stereoisomer' indicates a relative configuration known (trans) and the planar bond indicates the unknown absolute configuration. The same principles applies to 'CIS-single stereoisomer'.

Single stereoisomer a is assigned to the first eluting isomer in chiral HPLC, single stereoisomer b is assigned to the second eluting isomer in chiral HPLC.

INTERMEDIATES

Intermediate 1



To a stirred solution of 2-oxo-propanoic acid (157 mL, 2.23 mmol) in dry MeOH (100 mL) at 0° C., pyridine-2,3-diamine (20 g, 18 mmol) was added portionwise. The resulting solution was stirred at room temperature overnight, solvent was evaporated under reduced pressure and the suspension filtered. The solid was washed with MeOH, dried to obtain 14 g of title compound.

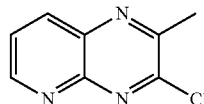
88

HPLC-MS (Method 6): $R_t=5$ min
MS: $m/z=162$ (M+H)⁺

Intermediate 2

5

10



15

20

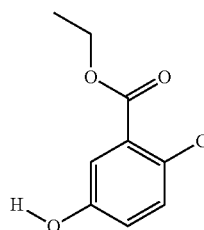
A mixture of Intermediate 1 (1 g) and phosphorus oxychloride (15 mL) was heated to 90° C. for 2.5 h. After cooling, the reaction mixture was carefully poured on ice, then neutralized with a saturated solution of Na₂CO₃ and diluted with DCM. Phases were separated, organics washed with a saturated solution of NaCl, dried over sodium sulphate and evaporated to obtain 0.95 g of the title compound.

HPLC-MS (Method 8): $R_t=4.54$ min
MS: $m/z=180$ (M+H)⁺

Intermediate 3

25

30



35

40

45

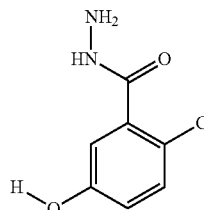
To a mixture of commercially available 2-chloro-5-hydroxybenzoic acid (4 g, 23.18 mmol) in dry EtOH (90 mL), concentrated sulphuric acid (1 mL, 17.62 mmol) was added. The mixture was stirred under reflux overnight, then solvent evaporated under reduced pressure and the residue dissolved with DCM. A saturated solution of NaHCO₃ was added, phases were separated, organics dried over sodium sulphate, filtered and evaporated to obtain 5 g of the corresponding 2-chloro-5-hydroxy-benzoic acid ethyl ester.

HPLC-MS (Method 2): $R_t=1.0$ min
MS: $m/z=201.6$ (M+H)⁺

Intermediate 4

50

55



60

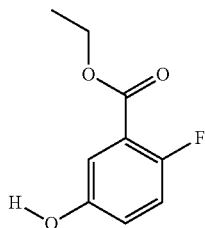
65

Intermediate 3 (5 g, 23.62 mmol) was dissolved in EtOH (100 mL) and hydrazine hydrate (13.0 mL, 262.12 mmol) was added. Mixture was stirred under reflux for 24 h, solvent evaporated and the crude treated with 20 mL of water. The white solid formed was filtered and washed with water and dried for 3 h at 60° C. over P₂O₅ to obtain 3.0 g of title compound.

HPLC-MS (Method 2): $R_t=0.53$ min
MS: $m/z=180$ (M+H)⁺

89

Intermediate 5

**90**

Intermediate 5 was prepared as described for Intermediate 3 starting from commercially available 2-fluoro-5-hydroxybenzoic acid (1 g, 6.41 mmol) to obtain 1.17 g of the title compound.

5

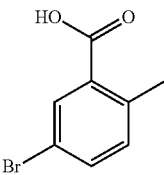
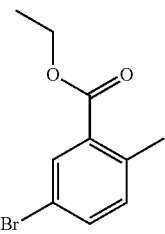
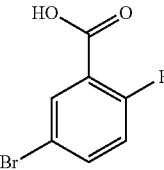
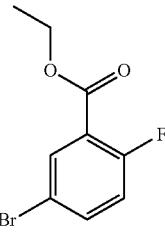
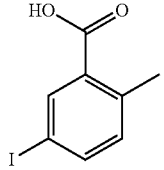
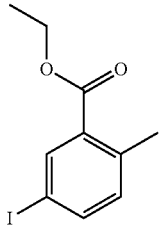
HPLC-MS (Method 2): $R_f=0.94$ minMS: $m/z=185.16$ ($M+H$)⁺

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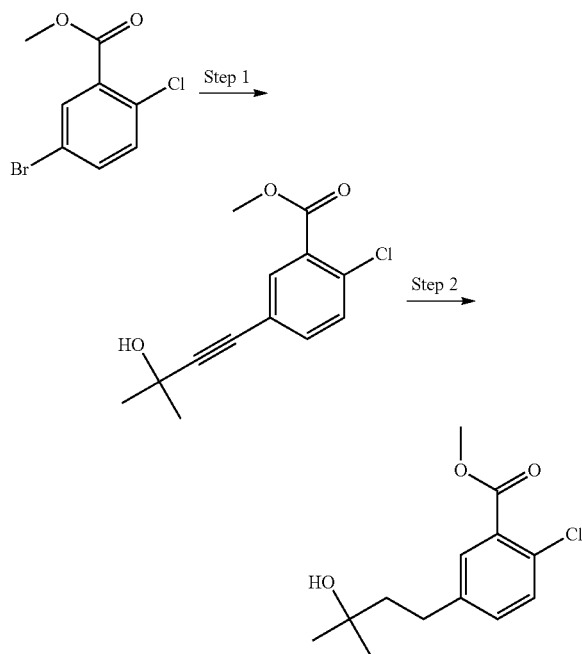
The following Ester Intermediates were prepared in analogy to Intermediate 3 starting from commercially available benzoic acids.

Starting benzoic acid	Ester Intermediate	MS m/z	R_f (min)	Method
	5a 	180 [M] ⁺	9.73	10
	5b 	203 [M + H] ⁺	1.2	2
	5c 	263 [M] ⁺	9.90	10
	5d 	310 [M] ⁺	10.47	10
	5e 	294 [M] ⁺	9.52	10

-continued

Starting benzoic acid	Ester Intermediate	MS m/z	R _f (min)	Method
	5f 	242 [M] ⁺	9.42	10
	5g 	246 [M] ⁺	8.84	10
	5h 	290 [M] ⁺	10.15	10

Intermediate 5i



Step 1:

Step 1 was performed in analogy to what reported in literature reference: Li, Yuanzhen et al. Organic Letters, 2007 vol. 9, #20 p. 4057-4060, starting from Ester Intermediate 5c.

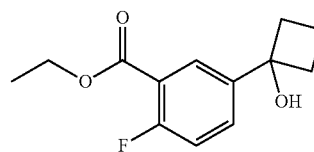
Step 2:

Intermediate obtained from Step 1 (0.5 g), was dissolved in toluene (10 mL). Wilkinson's catalyst RhCl(TPP)₃ (0.1 g) was added and the reaction mixture stirred at 60° C. under hydrogen atmosphere for 18 h. The reaction mixture was filtered on a celite pad and the solvent was removed under vacuum to obtain the desired product (0.4 g).

GC-MS (Method 10) R_f=11.55 min

MS: m/z=256 [M]⁺

Intermediate 5j




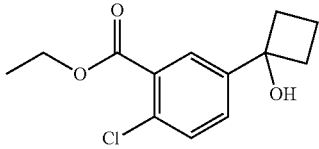
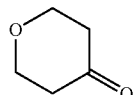
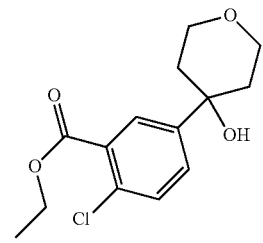

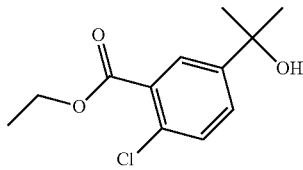
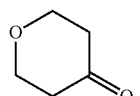
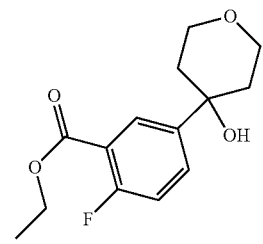
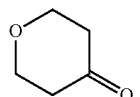
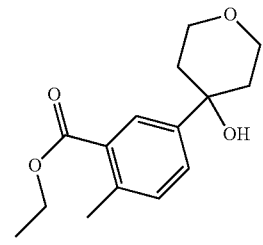
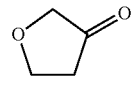
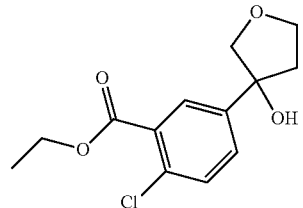
Under nitrogen atmosphere, starting Ester Intermediate 5e (5.0 g, 15.3 mmol) was dissolved in THF (40 mL), the reaction mixture was cooled to -50° C. and stirred for 10 minutes. Isopropyl-magnesium-chloride (11 mL of a 2M solution in THF) was added dropwise and the reaction mixture was stirred at -50° C. for 2 h. The reaction mixture was cooled to -78° C. and a solution of cyclobutanone (2.15 g, 30.6 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at -78° C. for 1 h, then warmed to room tempera-

ture and stirred for 18 h. The solvent was removed under vacuum, dichloromethane was added and the reaction mixture was washed with a saturated solution of NaHCO_3 . The organic phase was concentrated under vacuum and the crude product obtained was purified by flash chromatography (eluent from 90:10 to 80:20 Cy/EtOAc) to obtain the desired product (3.0 g).

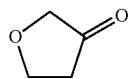
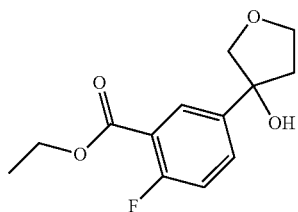
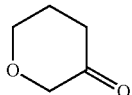
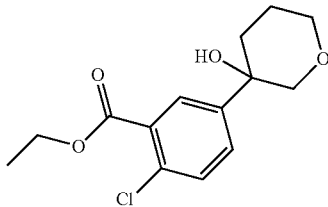
GC-MS (Method 10): $R_f=10.91$ min

MS: $m/z=210$ ($M-28$)⁺

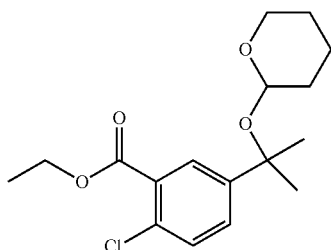
The following Ester Intermediates were prepared in analogy to Intermediate 5j and purified applying the most suitable purification technique, starting from the corresponding Starting Esters Intermediates and commercially available ketones.

Starting Ester inter- mediate	Starting ketone	Ester intermediate Structure	MS m/z	R_f (min)	Method
5d		5k 	255 [M + H] ⁺	4.23	16
5d		5l 	284 [M] ⁺	12.58	10
5d		5m 	243 [M + H] ⁺	1.04	2
5e		5n 	268 [M] ⁺	11.97	10
5h		5na 	264 [M] ⁺	12.18	10
5d		5q 	253 [M + H] ⁺	2.84	13

-continued

Starting Ester inter- mediate	Starting ketone	Ester intermediate Structure	MS m/z	R _f (min)	Method
5e		5r 	237 [M - 17] ⁺	2.68	13
5d		5s 	284 [M] ⁺	12.42	10

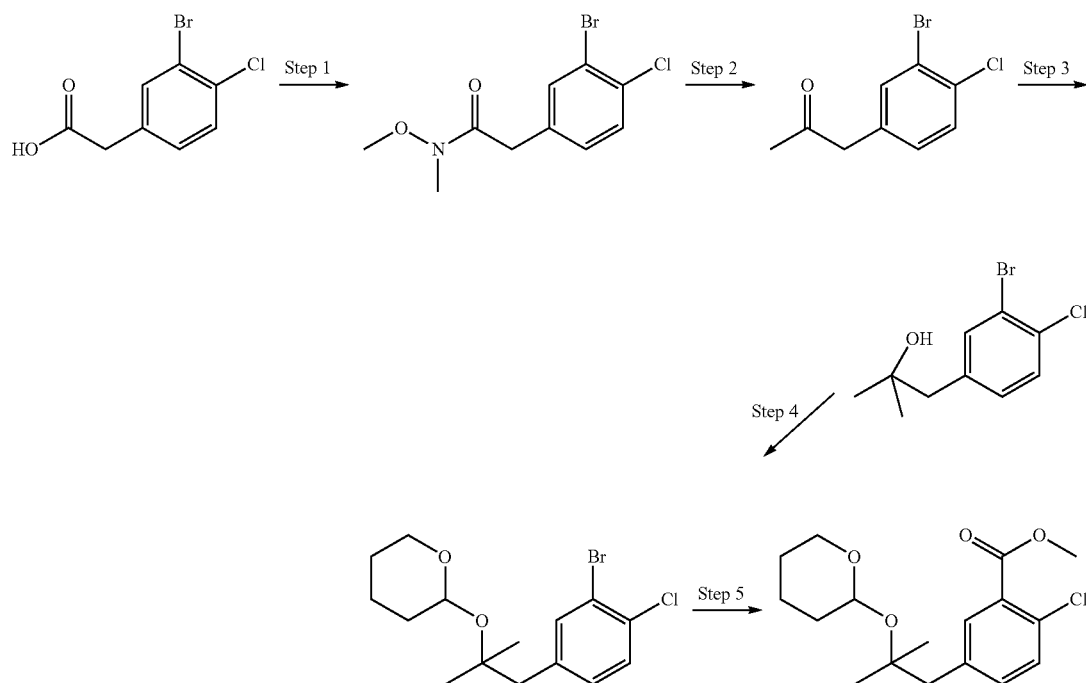
Intermediate 5o



25 To a solution of Ester Intermediate 5m (0.37 g, 1.52 mmol) in dichloromethane (9 mL), pyridinium-para-toluene-sulfonate (0.06 mg, 0.23 mmol) and 3,4-dihydro-2H-pyran (0.2 mL, 2.29 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was washed with water and the organic phase was concentrated under vacuum. Crude was purified by flash chromatography (eluent from 100:0 to 80:20 Cy/EtOAc) to obtain the desired product (0.4 g).

35 GC-MS (Method 10): R_f=12.52 min
MS: m/z=326 (M)⁺

Intermediate 5p



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Step 1:

Step 1 was performed in analogy to what reported in the literature reference: Duong, Hung A.; et al. *Angewandte Chemie, International Edition*, 2011 vol. 50, p. 463-466, starting from commercially available (3-bromo-4-chloro-phenyl)-

Step 2:

Under nitrogen atmosphere, a solution of Intermediate from Step 1 (0.24 g) in THF (10 mL) was stirred at -60°C ., methylmagnesium bromide was added dropwise and the reaction mixture was stirred at -78°C . to r.t. for 2 h. The reaction mixture was quenched with saturated ammonium chloride water solution and extracted with ethyl acetate twice, dried over sodium sulfate and concentrated under vacuum to get the crude product as colour-less oil.

Step 3:

Step 3 was performed in analogy to Step 2 starting from Intermediate obtained in Step 2.

Step 4:

Step 4 was performed in analogy to preparation of Intermediate 50, starting from Intermediate obtained in Step 3.

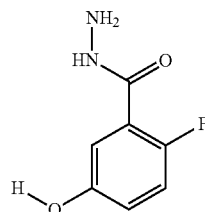
Step 5:

To a solution of the Intermediate obtained from Step 4 (15 g) in MeOH (150 mL), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (3.088 g) and triethylamine (22 g, 21.4 mL) were added and the reaction mixture was stirred at 80°C . under CO atmosphere for 36 h.

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The solvent was removed under vacuum and the crude product obtained was purified by flash chromatography to get the desired product.

Intermediate 6



Intermediate 6 (4,4 g) was prepared as described for Intermediate 4 and purified applying the most suitable purification technique, starting from Intermediate 5 (5.84 g, 0.03 mmol).

HPLC-MS (Method 2): $R_f=0.42$ minMS: $m/z=171.2$ ($M+H$)⁺

The following Hydrazone Intermediates were prepared in analogy to Intermediate 4 and purified applying the most suitable purification technique, starting from the corresponding Ester Intermediates.

Starting Ester intermediate		Hydrazone Intermediate Structure	MS m/z	R_f (min)	Method
5a	6a		167 [$M + H$] ⁺	0.47	17
5b	6b		188 [M] ⁺	9.47	10
5c	6c		249 [$M + H$] ⁺	1.98	13
5d	6d		296 [M] ⁺	11.78	10

-continued

Starting Ester intermediate		Hydrazide Intermediate Structure	MS m/z	R _t (min)	Method
5e	6e		281 [M + H] ⁺	1.83	9
5f	6f		229 [M + H] ⁺	1.80	9
5g	6g		233 [M + H] ⁺	1.55	9
5h	6h		277 [M + H] ⁺	1.94	9
5i	6i		256 [M + H] ⁺	0.68	2
5j	6j		225 [M + H] ⁺	0.56	2
5k	6k		241 [M + H] ⁺	0.59	2

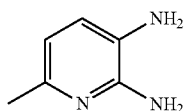
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Starting Ester intermediate	Hydrazone Intermediate Structure	MS m/z	R _f (min)	Method
5l 6l		271 [M + H] ⁺	0.57	2
5m 6m		228 [M] ⁺	11.79	10
5n 6n		255 [M + H] ⁺	0.43	2
5na 6na		251 [M + H] ⁺	0.57	2
5o 6o		313 [M + H] ⁺	0.85	2
5p 6p		327 [M + H] ⁺	0.90	2
5q 6q		257 [M + H] ⁺	0.49	13

-continued

Starting Ester intermediate	Hydrazone Intermediate Structure	MS m/z	R _f (min)	Method
5r	6r	241 [M + H] ⁺	0.44	2
5s	6s	271 [M + H] ⁺	0.58	2

Intermediate 7

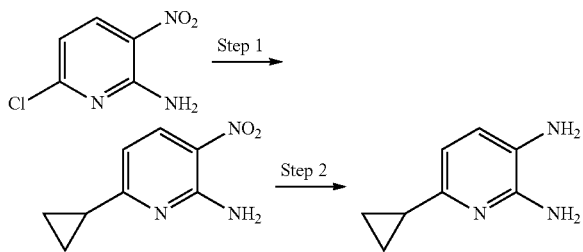


Commercially available 2-amino-6-methyl-3-nitropyridine (12 g, 78.36 mmol) was dissolved in a mixture of dry THF/MeOH (1:1, 60 mL) and hydrogenated in the presence of Pd/C (10%, 1.2 g) under 5 bar hydrogen atmosphere for 5 h. Catalyst was filtered, solvent evaporated under reduced pressure to obtain 7 g of the title compound.

HPLC-MS (Method 2): R_f=0.77 min

MS: m/z=154 (M+H)⁺

Intermediate 7a



Step 1:

2-Amino-6-chloro-3-nitro-pyridine (20 g, 115 mmol), cyclopropylboronic acid (12.8 g, 150 mmol), tricyclohexylphosphine (3.2 g, 11.5 mmol), 2,6-di-tert-butyl-4-methylphenol (5.08 g, 23 mmol), palladium acetate (1.3 g, 5.7 mmol) and tri-potassium-phosphate (73 g, 346 mmol) were suspended in toluene (40 mL) and water (2 mL). The reaction mixture was stirred at reflux for 18 h, diluted with ethyl acetate and washed with water. The organic phase was separated, concentrated under vacuum and dried over sodium sulfate. The crude product obtained was purified by flash chromatography (eluent from 90:10 to 45:55 Cy/EtOAc) to obtain the desired product (10.6 g).

GC-MS (Method 10): R_f=10.54 min

MS: m/z=179 (M)⁺

Step 2:

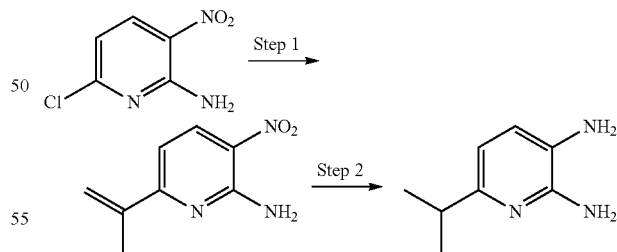
To a solution of Intermediate from Step 1 (6 g, 19 mmol) in absolute EtOH (120 mL), zinc (13.7 g, 209 mmol) and ammonium chloride (30.8 g, 573 mmol) were added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered on a celite pad, the solvent was removed under vacuum and the crude product obtained was purified by flash chromatography (eluent 90:10 dichloromethane/MeOH) to obtain the desired product (2.4 g).

HPLC-MS (Method 9): R_f=1.42 min

MS: m/z=150 (M+H)⁺

Intermediate 7b

45



Step 1:

Step 1 was performed in analogy to what described in Step 1 in the preparation of Intermediate 7a, starting from commercially available 2-isopropenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane.

Step 2:

Intermediate from Step 1 (5 g, 26.5 mmol) was dissolved in 20 mL of methanol, Pd/C (0.25 g) was added and the reaction mixture was stirred under hydrogen atmosphere (4 bar) for 2

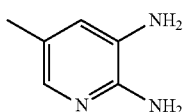
105

h at room temperature. The reaction mixture was filtered on a celite pad and the solvent was removed under vacuum to give the desired product (3 g).

GC-MS (Method 10): R_f =8.91 min

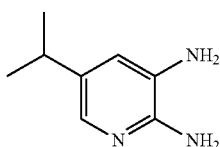
MS: m/z =151 (M)⁺

Intermediate 7c



Intermediate 7c (3.99 g) was prepared in analogy to Intermediate 7 and purified applying the most suitable purification technique, starting from commercially available 2-amino-3-nitro-5-picoline (5.0 g, 32.65 mmol).

Intermediate 7d

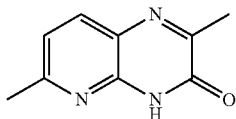


Intermediate 7d (4 g) was prepared in analogy to Intermediate 7b and purified applying the most suitable purification technique, starting from commercially available 2-amino-5-chloro-3-nitro-pyridine (5 g, 26.5 mmol).

HPLC-MS (Method 2): R_f =0.6 min

MS: m/z =152 ($M+H$)⁺

Intermediate 8



To stirred solution of 2-oxo-propanoic acid (40.8 mL, 587 mmol) in dry MeOH (130 mL) at 0° C., 6-methyl-pyridine-2,3-diamine (Intermediate 7, 6.8 g, 55.2 mmol) dissolved in dry MeOH (40 mL) was added dropwise. The solution was stirred at room temperature overnight then solvent was evapo-

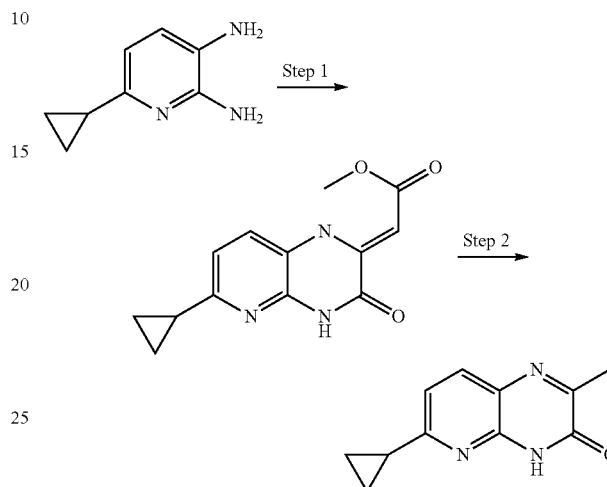
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rated under reduced pressure and the resulting suspension filtered. The solid was washed with MeOH, dried to obtain 1.35 g of title compound.

HPLC-MS (Method 9): R_f =1.31 min

MS: m/z =176 ($M+H$)⁺

Intermediate 8a



Step 1:

Intermediate 7a (2.4 g, 15.2 mmol) was dissolved in absolute EtOH and stirred at 0° C., Dimethylacetylenedicarboxylate (2.4 g, 16.8 mmol) was added dropwise and the reaction mixture was allowed to react room temperature for 18 h. The solid formed was filtered, washed with EtOH, Ethyl Ether and dried in vacuum to give the desired product (3 g).

HPLC-MS (Method 13): R_f =3.16 min

MS: m/z =260 ($M+H$)⁺

Step 2:

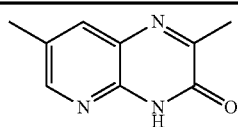
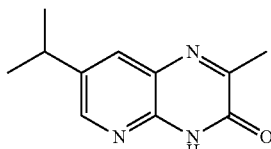
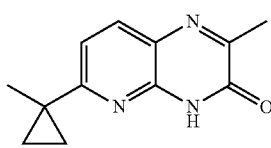
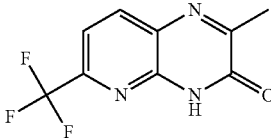
Intermediate obtained from Step 1 (3 g 0.01 mol) was dissolved in a sodium hydroxide water solution (1.36 g, 0.03 mol in 50 mL) and the reaction mixture was reflux for 2 h. pH was adjusted to 2-3 and the reaction mixture was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, concentrated under vacuum. The crude product obtained was purified by flash chromatography (eluent from 80:20 to 20:80 Cy/EtOAc) to obtained the desired product (2.0 g).

HPLC-MS (Method 13): R_f =2.46 min

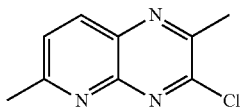
MS: m/z =202 ($M+H$)⁺

The following Amide Intermediates were prepared in analogy to Amide Intermediate 8a and purified applying the most suitable purification technique, starting from the corresponding Di-amine Intermediates.

Starting	Amide Intermediate				
Di-amine	Structure	MS m/z	R_f (min)	Method	
Intermediate					
7b	8b	204 [$M + H$] ⁺	2.48	13	

Starting Di-amine Intermediate	Amide Intermediate Structure	MS m/z	R _f (min)	Method
7c	8c 	176 [M + H] ⁺	1.88	13
7d	8d 	204 [M + H] ⁺	0.78	2
6-(1-Methyl-cyclopropyl)-pyridine-2,3-diamine (commercially available)	8e 	216 [M + H] ⁺	4.96	17
6-trifluoromethyl-pyridine-2,3-diamine (commercially available)	8f 	229 [M] ⁺	9.42	10

Intermediate 9



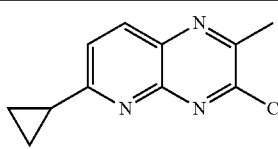
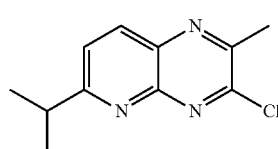
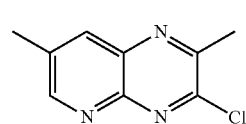
A mixture of Amide intermediate 8 (1.35 g, 7.71 mmol) and phosphorus oxychloride (16 mL) was heated to 90° C. for 3 h. After cooling, solvent was reduced under reduced pres-

sure, the reaction mixture was carefully poured on ice and neutralized with a saturated solution of Na₂CO₃. DCM was added, phases were separated, organics washed with a saturated solution of NaCl, dried over sodium sulphate and evaporated to obtain 1.39 g of the title compound.

HPLC-MS (Method 8): R_f=0.84 min

MS: m/z=194.6 (M+H)⁺

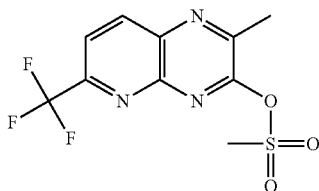
The following Chloride Intermediates were prepared in analogy to Chloride Intermediate 9 and purified applying the most suitable purification technique, starting from the corresponding Amide Intermediates. Heating temperature reported in Table.

Starting Amide Intermediate	Chloride Intermediate Structure	Heating Temperature	MS m/z	R _f (min)	Method
8a	9a 	55° C.	220 [M + H] ⁺	1.01	2
8b	9b 	80° C.	222 [M + H] ⁺	3.18	13
8c	9c 	90° C.	194 [M + H] ⁺	2.52	13

-continued

Starting Amide Intermediate	Chloride Intermediate Structure	Heating Temperature	MS m/z	R _f (min)	Method
8d	9d	55° C.	222 [M + H] ⁺	3.19	13
8e	9e	80° C.	234 [M + H] ⁺	1.15	2

Intermediate 9f



Intermediate 8f (1.35 g, 5.9 mmol) and N,N-diisopropylethylamine (2.28 g, 3 mmol) were dissolved in DMF (10 mL).

20 The reaction mixture was cooled to 0° C. and methanesulfonylchloride (0.74 g, 6.48 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 4 h. Ammonium chloride saturated water solution was added and the reaction mixture was extracted with
25 dichloromethane. The organic phase was washed with citric acid (10% water solution), dried over sodium sulfate and concentrated under vacuum, to give the desired product (1.5 g).

HPLC-MS (Method 13): R_f=3.09 min

30 MS: m/z=308 (M+H)⁺

The following Intermediates were prepared based on well known reported procedures starting from commercially available starting materials.

Intermediate	Structure	Reference
10 Toluene-4-sulfonic acid 3-hydroxy-3-methyl-butyl ester		Bioorganic & Medicinal Chemistry Letters (2007), 17(22), 6164-6168
11 Toluene-4-sulfonic acid 3-hydroxy-butyl ester		Bioorganic & Medicinal Chemistry, 18(4), 1665-1675; 2010
12 Toluene-4-sulfonic acid 3,3,3-trifluoro-propyl ester		US 2009-564132
13 Toluene-4-sulfonic acid tetrahydropyran-4-yl ester		WO 2011-20767
14 Toluene-4-sulfonic acid 4,4-difluoro-cyclohexyl ester		WO 2008-119663

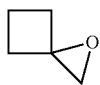
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Intermediate	Structure	Reference
15 Toluene-4-sulfonic acid tetrahydro-furan-3-yl ester		WO 2010-023594
16 Toluene-4-sulfonic acid (S)-(tetrahydro-furan-3- yl) ester		WO 2011-061590
17 Toluene-4-sulfonic acid (R)-(tetrahydro-furan-3- yl) ester		WO 2010-102512
18 Toluene-4-sulfonic acid tetrahydro-furan-3- ylmethyl ester		WO 2011-084402
19 tert-Butyl-(R)-2-chloro- 1-methyl-ethoxy)- diphenyl-silane		Tetrahedron Letters (1982), 23(25), 2543- 6.
20 tert-Butyl-(S)-2-chloro- 1-methyl-ethoxy)- diphenyl-silane		Tetrahedron Letters (1982), 23(25), 2543- 6.
21 2-((S)-2-Chloro-1- methyl-ethoxy)-tetra- hydro-pyran		Tetrahedron Letters (1982), 23(25), 2543- 6.
26 Toluene-4-sulfonic acid 3-methyl-oxetan-3- ylmethyl ester		Synthetic Communications (2011), 41(17), 2539- 2543

-continued

Intermediate	Structure	Reference
27	Toluene-4-sulfonic acid 1-(tetrahydro-pyran-4-yl)-ethyl ester	Journal of Organometallic Chemistry (1978), 150(2), 179-85
28	Toluene-4-sulfonic acid 1,4-dioxaspiro[4.5]dec-8-yl ester	WO 2010-006086
29	Toluene-4-sulfonic acid 3-hydroxy-cyclopentyl ester	US 2007-0049537

Intermediate 29a

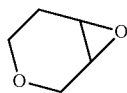


Literature Reference: Journal of Organic Chemistry USSR (English Translation), 1989 vol. 25, #6.1 p. 1019-1025).

Epoxide Intermediate 29a (4 g) was prepared in analogy to what described in WO2010/47956 A1, starting from methylene cyclobutane (5 g, 73 mmol).

GC-MS (Method 10) R_f =2.70 min
 $[M]^+=83$

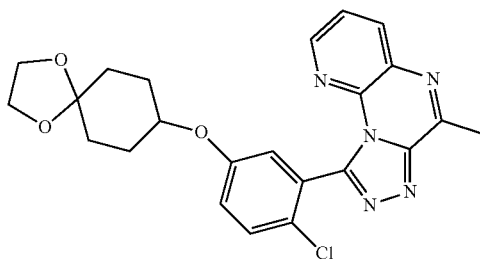
Intermediate 29b



Epoxide Intermediate 29b (1 g) was prepared in analogy to what described in WO2013/55577 A1 starting from 3,6-Di-hydro-2H-pyran (2 g, 23.78 mmol).

GC-MS (Method 10) R_f =8.10 min
 $[M]^+=99$

Intermediate 29c

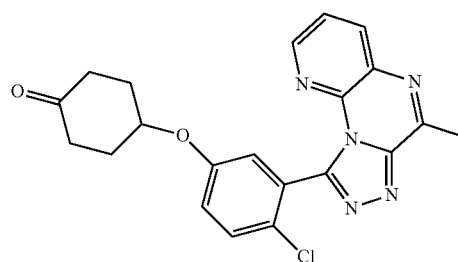


To a solution of Example 1 (0.2 g, 0.67 mmol) in dry DMF (3 mL), cesium carbonate (0.63 g, 1.92 mmol) and Intermediate 28 (0.41 g, 1.28 mmol) were added. Mixture was heated at 80° C. for 1 h, then solvent evaporated under reduced pressure and the residue dissolved in DCM and washed with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.21 g of the title compound.

HPLC-MS (Method 2): R_f =1.12 min

MS: m/z =452 (M+H)⁺

Intermediate 30



To a solution of Intermediate 29c (0.21 g, 0.46 mmol) in acetone (10 mL), a 4M solution of HCl (1 mL) was added and mixture stirred at room temperature for 2 h. Solvent was evaporated under reduced pressure, the residue treated with DCM, washed with a saturated solution of NaHCO₃. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 90:10 to 50:50 Cy/EtOAc) to obtain 0.18 g of the title compound.

HPLC-MS (Method 2): R_f =1.09 min

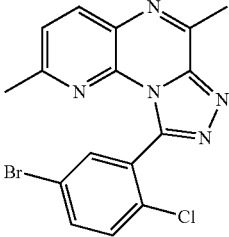
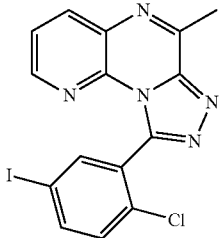
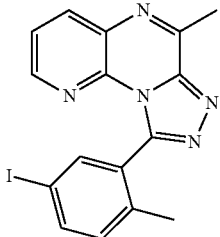
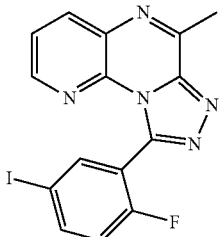
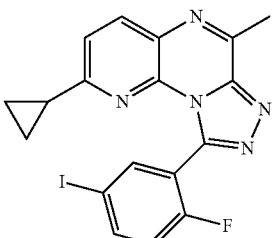
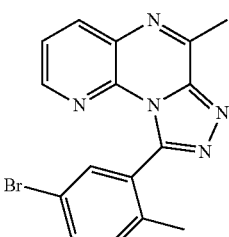
MS: m/z =410 (M+H)⁺

115

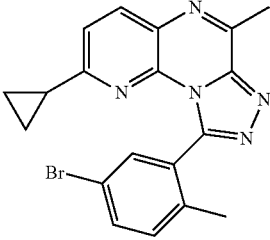
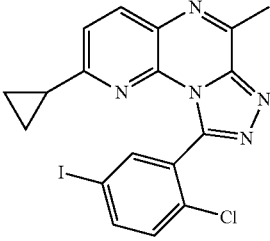
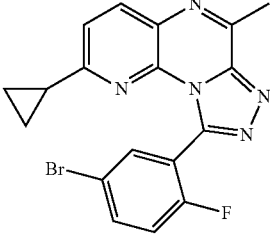
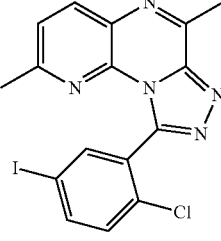
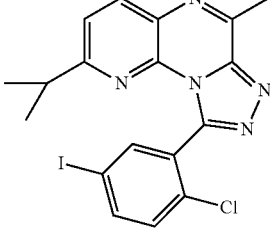
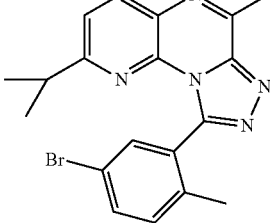
The following intermediates were prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from the corresponding Chloride and

116

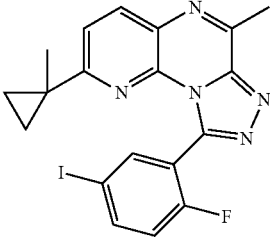
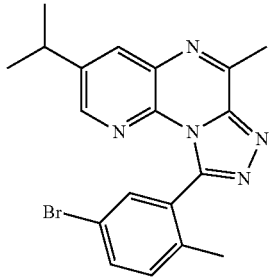
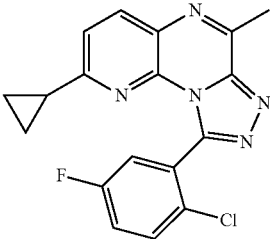
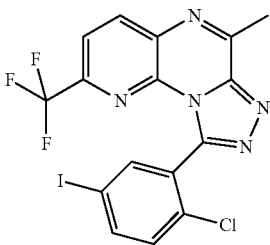
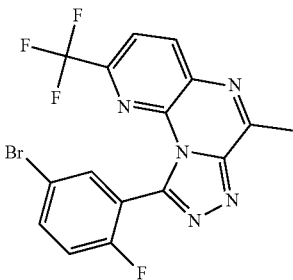
Idrazide intermediates:

Chloride Intermediate	Hydrazide	Intermediate Structure	MS m/z	R _t (min)	Method
9	6c	30a	388 [M + H] ⁺	3.58	13
					
2	6d	30b	422 [M + H] ⁺	1.07	2
					
2	6h	30c	402 [M + H] ⁺	3.00	9
					
2	6e	30d	406 [M + H] ⁺	3.02	9
					
9a	6e	30e	446 [M + H] ⁺	3.78	13
					
2	6f	30f	354 [M + H] ⁺	3.35	13
					

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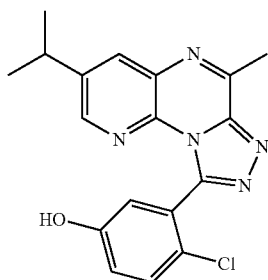
Chloride Inter- mediate	Hydrazide	Intermediate Structure	MS m/z	R _t (min)	Method
9a	6f	30g	394 [M + H] ⁺	3.69	13
					
9a	6d	30h	462 [M + H] ⁺	3.81	13
					
9a	6g	30i	398 [M + H] ⁺	3.72	13
					
9	6d	30j	436 [M + H] ⁺	3.64	13
					
9b	6d	30k	464 [M + H] ⁺	3.99	13
					
9b	6f	30l	396 [M + H] ⁺	3.85	13
					

-continued

Chloride			Intermediate Structure	MS m/z	R _t (min)	Method
Inter- mediate	Hydrazide					
9e	6e	30m		460 [M + H] ⁺	1.29	2
9d	6f	30n		397 [M + H] ⁺	1.27	2
9a	6b	30o		354 [M + H] ⁺	3.53	13
9f	6d	30r		490 [M + H] ⁺	1.25	2
9f	6g	30s		427 [M + H] ⁺	1.15	2

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Intermediate 30p

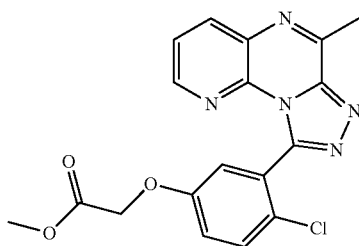


Intermediate 30p (0.26 g) was prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from Chloride Intermediate 9d (0.25 g, 1.01 mmol) and Hydrazide Intermediate 4 (0.19 g, 1.01 mmol).

HPLC-MS (Method 2): $R_f=1.01$ min

MS: $m/z=354$ (M+H)⁺

Intermediate 31



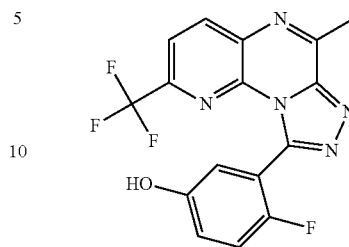
To a solution of Example 1 (0.4 g, 1.3 mmol) in dry DMF (4 mL), cesium carbonate (0.85 g, 2.62 mmol) and methylbromoacetate (0.152 mL, 1.56 mmol) were added. Mixture was stirred at room temperature overnight, solvent evaporated and the residue treated with EtOAc. A saturated solution of NH₄Cl was added, phases were separated and evaporated. The crude was purified by flash chromatography (eluent from 50:50 to 0:100 Cy/EtOAc) to obtain 0.29 g of the title compound.

HPLC-MS (Method 13): $R_f=3.06$ min

MS: $m/z=384$ (M+H)⁺

122

Intermediate 32



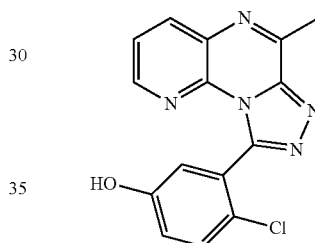
Intermediate 32 (0.5 g) was prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from Intermediate 9f (0.9 g, 2.52 mmol) and Hydrazide Intermediate 6 (0.47 g, 2.77 mmol).

HPLC-MS (Method 13) $R_f=3.11$ min

MS: $m/z=380$ (M+H)⁺

Exemplary Embodiments:

Example 1



Intermediate 2 (0.60 g, 3.34 mmol) and Intermediate 4 (0.62 g, 3.34 mmol) were suspended in cyclohexanol (5 mL) and heated under reflux for 2 h. The resulting solution was cooled and solvent evaporated under reduced pressure and the residue purified by flash chromatography (eluent 95:5 DCM/EtOH) to obtain 0.95 g of the title compound.

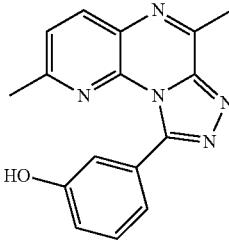
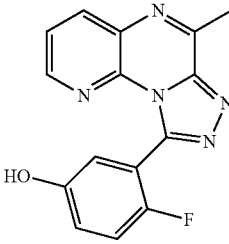
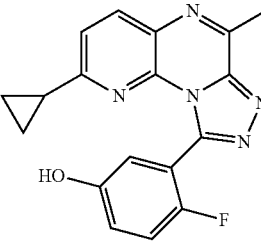
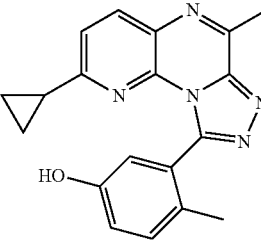
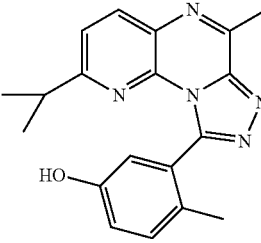
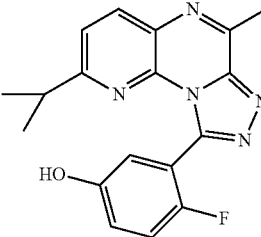
HPLC-MS (Method 9): $R_f=2.17$ min

MS: $m/z=312$ (M+H)⁺

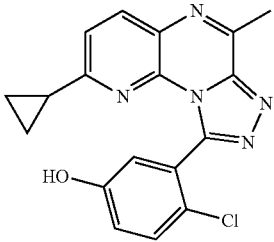
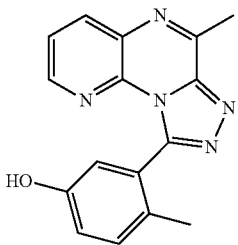
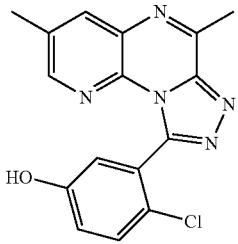
The following Examples were prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from the corresponding Chloride Intermediates and Hydrazide Intermediates:

Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex.	Structure	MS m/z [M + H] ⁺	R_f (min)	Method
9	4	2		326	0.93	2

-continued

Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex.	Structure	MS m/z [M + H] ⁺	R _f (min)	Method
9	3-hydroxy-benzhydrazide (commercially available)	3		292	2.62	13
2	6	4		296	0.79	13
9a	6	5		336	2.97	13
9a	6a	6		226	2.93	13
9b	6a	7		334	3.16	13
9b	6	8		338	3.14	13

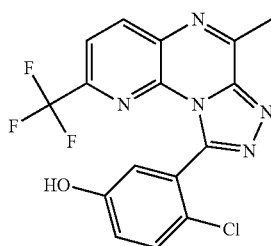
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Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex.	Structure	MS m/z [M + H] ⁺	R _f (min)	Method
9a	4	9		352	2.59	9
2	6a	10		292	2.03	13
9c	4	11		326	2.96	13

Example 12

Example 12a

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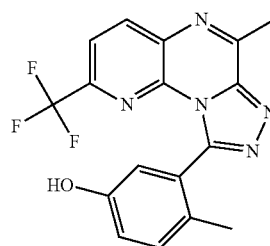


Example 12 (0.04 g) was prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from Intermediate 9f (0.3 g, 0.68 mmol) and Hydrazide Intermediate 4 (0.27, 0.68 mmol).

HPLC-MS (Method 13) R_f=3.11 min

MS: m/z=380 (M+H)⁺

60



Example 12a (0.15 g) was prepared in analogy to Example 12 and purified applying the most suitable purification technique, starting from the Hydrazide Intermediate 6a (0.23 g, 1.45 mmol).

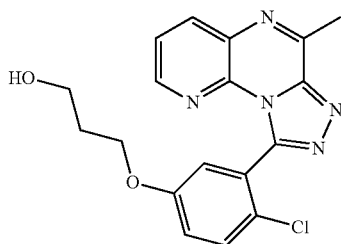
HPLC-MS (Method) R_f=3.00 min

MS: m/z=360 (M+H)⁺

65

127

Example 13

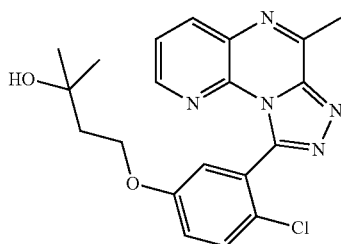


To a solution of Example 1 (0.1 g, 0.24 mmol) in dry ACN (3 mL), cesium carbonate (0.2 g) and commercially available 3-chloro-1-propanol (0.04 mL) were added. Mixture was heated at 80° C. for 1 h, then solvent evaporated under reduced pressure and the residue dissolved in DCM and washed with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 94:6 DCM/EtOH) to obtain 0.02 g of the title compound.

HPLC-MS (Method 8) R_t =5.23 min

MS: m/z =370 (M+H)⁺

Example 14



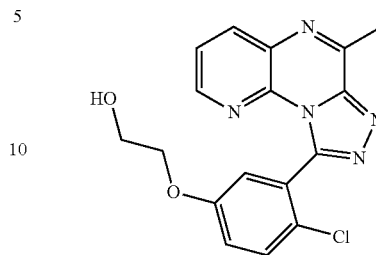
To a solution of Example 1 (0.05 g, 0.16 mmol) in dry DMF (3 mL), Intermediate 10 (0.05 g, 0.018 mmol) and cesium carbonate (0.08 g, 0.24 mmol) were added and mixture heated at 100° C. for 2 h. Solvent was evaporated, the residue was dissolved with DCM, washed with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 70:30 to 20:80 Cy/EtOAc) to obtain 0.025 g of the title compound.

HPLC-MS (Method 9): R_t =2.57 min

MS: m/z =398 (M+H)⁺

128

Example 15

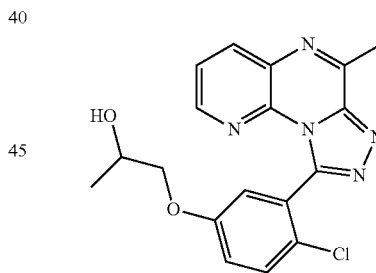


To a solution of Example 1 (0.08 g, 0.16 mmol) in dry ACN (3 mL), commercially available 2-bromo-ethanol (0.65 g, 0.52 mmol) and cesium carbonate (0.5 g, 1.54 mmol) were added and mixture heated at 80° C. for 48 h. Solvent was evaporated, the residue was dissolved with DCM, washed with 1N solution of NaOH and then with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 97:3 DCM/EtOH) to obtain 0.04 g of the title compound.

HPLC-MS (Method 6): R_t =8.75 min

MS: m/z =356 (M+H)⁺

Example 16



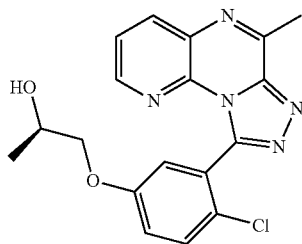
To a solution of Example 1 (0.05 g, 0.16 mmol) in dry DMF (3 mL), commercially available 1-bromo-2-propanol (0.09 g, 0.64 mmol) and potassium tert-butoxide (0.1 g, 0.96 mmol) were added and mixture heated at 130° C. for 8 h. Solvent was evaporated, the residue was dissolved with DCM, washed with 1N solution of NaOH and then with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 97:3 DCM/EtOH) to obtain 0.05 g of the title compound.

HPLC-MS (Method 9): R_t =2.23 min

MS: m/z =370 (M+H)⁺

129

Example 17

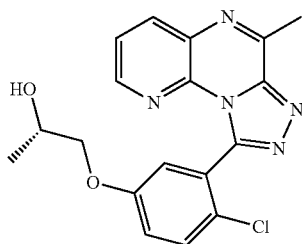


To a solution of Example 1 (0.085 g, 0.27 mmol) in dry DMF (3 mL), commercially available (R)-1-chloro-2-propanol (0.052 g, 0.55 mmol) and potassium tert-butoxide (0.093 g, 0.82 mmol) were added and mixture heated at 130° C. for 48 h. Solvent was evaporated, the residue was dissolved with DCM, washed with 1N solution of NaOH and then with a saturated solution of NaCl. Phases were separated, organics dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 97:3 DCM/EtOH) to obtain 0.0085 g of the title compound.

HPLC-MS (Method 9): R_t =2.22 min

MS: m/z =370 (M+H)⁺

Example 18

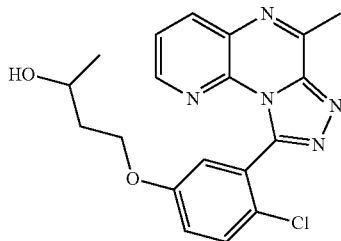


Example 18 was prepared as described for Example 17 starting from Example 1 (0.085 g, 0.27 mmol) and commercially available (S)-1-chloro-2-propanol. The residue was purified by flash chromatography (eluent from 100:0 to 90:10 DCM/MeOH) to obtain 0.045 g of the title compound.

HPLC-MS (Method 9): R_t =2.19 min

MS: m/z =370 (M+H)⁺

Example 19



To a solution of Example 1 (0.115 g, 0.37 mmol) in dry DMF (3 mL), cesium carbonate (0.36 g, 1.11 mmol) and Intermediate 11 (0.09 g, 0.37 mmol) were added and mixture heated at 100° C. for 4 h. Solvent was evaporated, the residue was dissolved with DCM, washed with a saturated solution of NaCl. Phases were separated, organics dried over sodium

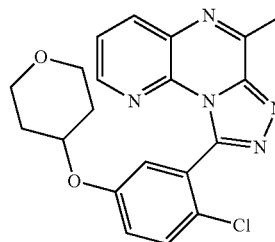
130

sulphate and evaporated. The residue was purified by flash chromatography (eluent from 100:0 to 80:20 DCM/EtOH) to obtain 0.025 g of the title compound.

HPLC-MS (Method 9): R_t =2.4 min

MS: m/z =384 (M+H)⁺

Example 20

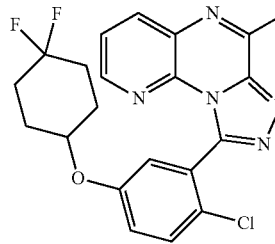


Example 20 was prepared as described for Example 19, starting from Example 1 (0.08 g, 0.26 mmol) and Intermediate 13 (0.2 g, 0.78 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.032 g of the title compound.

HPLC-MS (Method 9): R_t =2.65 min

MS: m/z =396 (M+H)⁺

Example 21

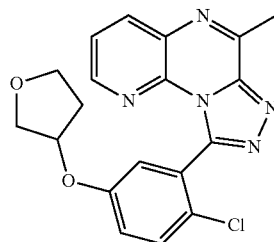


Example 21 was prepared as described for Example 20, starting from Example 1 (0.065 g, 0.21 mmol) and Intermediate 14 (0.12 g, 0.42 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.035 g of the title compound.

HPLC-MS (Method 9): R_t =3.32 min

MS: m/z =430 (M+H)⁺

Example 22



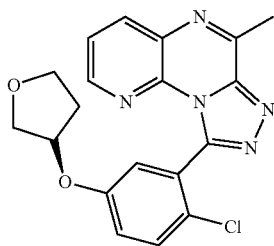
Example 22 was prepared as described for Example 20, starting from Example 1 (0.1 g, 0.32 mmol) and Intermediate 15 (0.093 g, 0.38 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.032 g of the title compound.

HPLC-MS (Method 13): R_t =3.03 min

MS: m/z =382 (M+H)⁺

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Example 23

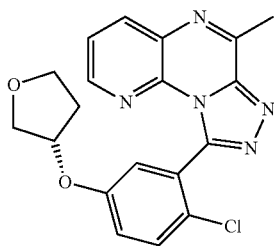


Example 23 was prepared as described for Example 20, starting from Example 1 (0.1 g, 0.32 mmol) and Intermediate 17 (0.093 g, 0.38 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.02 g of the title compound.

HPLC-MS (Method 13): R_f =3.07 min

MS: m/z =382 (M+H)⁺

Example 24

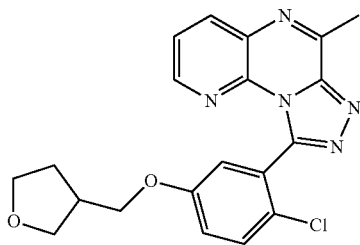


Example 24 was prepared as described for Example 20, starting from Example 1 (0.1 g, 0.32 mmol) and Intermediate 16 (0.093 g, 0.38 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.03 g of the title compound.

HPLC-MS (Method 13): R_f =3.05 min

MS: m/z =382 (M+H)⁺

Example 25



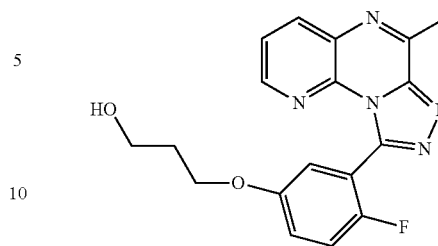
Example 25 was prepared as described for Example 20, starting from Example 1 (0.1 g, 0.32 mmol) and Intermediate 18 (0.097 g, 0.38 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.03 g of the title compound.

HPLC-MS (Method 13): R_f =3.18 min

MS: m/z =396 (M+H)⁺

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Example 26

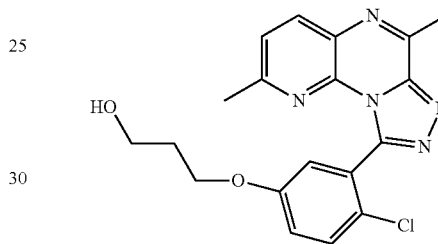


Example 26 was prepared as described for Example 20, starting from Example 4 (0.08 g, 0.27 mmol) and commercially available 3-chloro-1-propanol (0.052 g, 0.54 mmol). The crude was purified by flash chromatography (eluent from 100:0 to 97:3 DCM/EtOH) to obtain 0.052 g of the title compound.

HPLC-MS (Method 13): R_f =2.71 min

MS: m/z =354 (M+H)⁺

Example 27

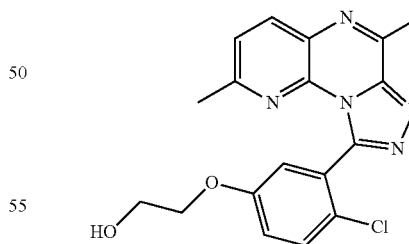


Example 27 was prepared as described for Example 20, starting from Example 2 (0.133 g, 80% content, 0.32 mmol) and commercially available 3-chloro-1-propanol (0.046 g, 0.49 mmol). The crude was purified by prep-HPLC (Method 11). Fractions containing the pure compound were combined and evaporated to reduced volume, diluted with DCM and treated with a saturated solution of sodium carbonate. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.039 g of the title compound.

HPLC-MS (Method 9): R_f =2.46 min

MS: m/z =384 (M+H)⁺

Example 28



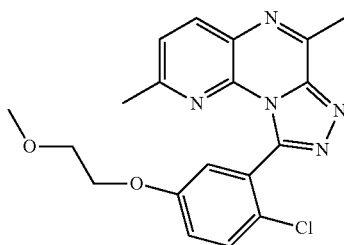
Example 28 was prepared as described for Example 20, starting from Example 2 (0.133 g, 80% content, 0.32 mmol) and commercially available 2-bromo-ethanol (0.061 g, 0.49 mmol). The crude was purified by prep-HPLC (Method 12). Fractions containing the pure compound are combined and evaporated to reduced volume, diluted with DCM and treated with a saturated solution of sodium carbonate. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.025 g of the title compound.

HPLC-MS (Method 9): R_f =2.35 min

MS: m/z =370 (M+H)⁺

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Example 29

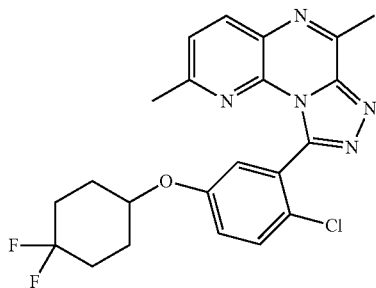


To a solution of Example 2 (0.07 g, 0.20 mmol) and commercially available 2-bromo-methylether (0.057 g, 0.41 mmol) in dry DMF (3 mL), cesium carbonate (0.199 g, 0.61 mmol) was added and the mixture heated at 100° C. for 1 h. Solvent was evaporated under reduced pressure, the residue dissolved with DCM and treated with water. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 80:20 to 40:60 hexane/ 25 EtOAc) to obtain 0.023 g of the title compound.

HPLC-MS (Method 9): R_f =2.82 min

MS: m/z =384 (M+H)⁺

Example 30



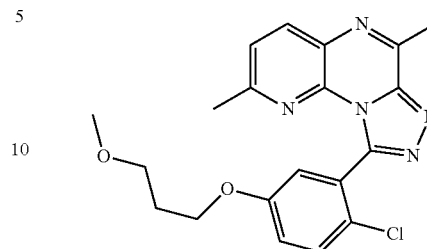
To a solution of Example 2 (0.07 g, 0.20 mmol) and Intermediate 14 (0.12 g, 0.41 mmol) in dry DMF (3 mL), cesium carbonate (0.2 g, 0.61 mmol) was added and the mixture heated at 90° C. for 2 h. Solvent was evaporated under reduced pressure, the residue dissolved with DCM and treated with water. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 80:20 to 40:60 hexane/EtOAc) and then further purified by prep-HPLC (Method 14). Fractions containing the pure compound were combined and evaporated to reduced volume, diluted with DCM. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.047 g of the title compound.

HPLC-MS (Method 9): R_f =3.56 min

MS: m/z =444 (M+H)⁺

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Example 31

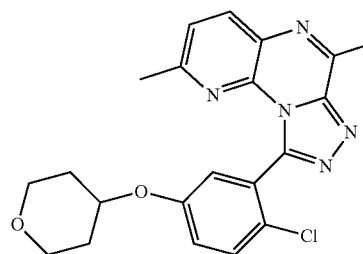


Example 31 was prepared as described for Example 30 starting from Example 2 (0.07 g, 0.20 mmol) and commercially available 1-bromo-3-methoxy-propane (0.063 g, 0.41 mmol). After heating for 3 h at 100° C. in dry DMF (3 mL), solvent was evaporated under reduced pressure, the residue dissolved with DCM and treated with water. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 88:12 to 0:100 Cy/EtOAc) to obtain 0.043 g of the title compound.

HPLC-MS (Method 13): R_f =3.55 min

MS: m/z =398 (M+H)⁺

Example 32



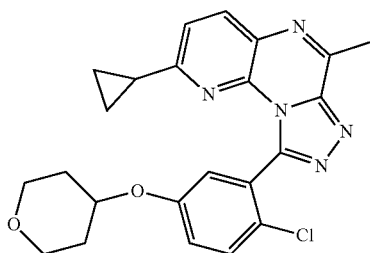
Example 32 was prepared as described for Example 31 starting from Example 2 (0.09 g, 0.26 mmol) and Intermediate 13 (0.20 g, 0.78 mmol). Solvent was evaporated under reduced pressure, the residue dissolved with DCM and washed with 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 88:12 to 0:100 Cy/EtOAc) to obtain 0.037 g of the title compound.

HPLC-MS (Method 9): R_f =2.95 min

MS: m/z =410 (M+H)⁺

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Example 32a

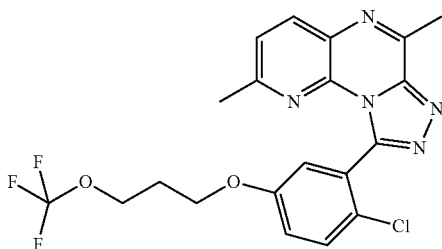


Example 32a (0.06 g) was prepared in analogy to Example 32 and purified applying the most suitable purification technique, starting from Example 9 (0.08 g, 0.23 mmol).

HPLC-MS (Method 16): R_f =4.51 min

MS: m/z =436 (M+H)⁺

Example 33

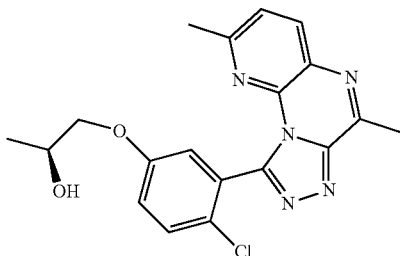


Example 33 was prepared as described for Example 31 starting from Example 2 (0.07 g, 0.20 mmol) and commercially available 1-bromo-3-trifluoromethoxypropane (0.084 g, 0.41 mmol). Solvent was evaporated under reduced pressure, the residue dissolved with DCM and washed with water. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 88:12 to 0:100 Cy/EtOAc) and then further purified by prep-HPLC (Method 14). Fractions containing the pure compound were combined and evaporated to reduced volume, diluted with DCM. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.047 g of the title compound. chromatography (eluent from 88:12 to 0:100 Cy/EtOAc) to obtain 0.037 g of the title compound.

HPLC-MS (Method 13): R_f =1.06 min

MS: m/z =452 (M+H)⁺

Example 34



To a solution of Example 2 (0.082 g, 0.25 mmol) in dry DMF (3 mL), potassium tert-butoxide (0.084 g, 0.65 mmol)

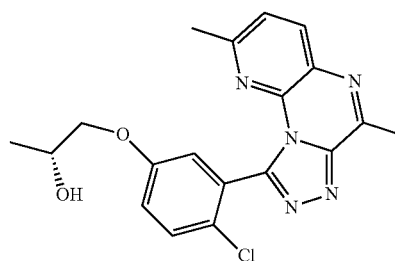
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and Intermediate 20 (0.176 g, 0.50 mmol) were added. The resulting solution was heated at 120° C. for 5 h. The mixture was left at room temperature for 24 h. Solvent was evaporated under reduced pressure, the residue dissolved in DCM and treated with a 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 20:80 to 0:100 ACN/H₂O) to obtain 0.033 g of the title compound.

HPLC-MS (Method 9): R_f =2.98 min

MS: m/z =384 (M+H)⁺

Example 35

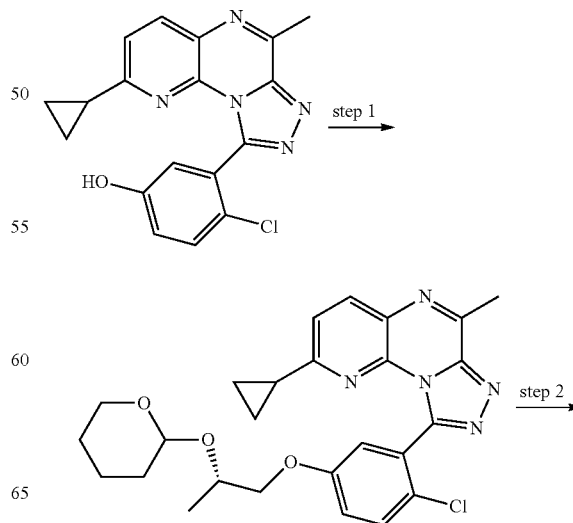


To a solution of Example 2 (0.095 g, 0.29 mmol) in dry DMF (3 mL), potassium tert-butoxide (0.074 g, 0.22 mmol) and Intermediate 19 (0.204 g, 0.58 mmol) were added. The resulting solution was heated at 120° C. for 5 h. Solvent was evaporated under reduced pressure, the residue dissolved in DCM and treated with a 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 80:20 to 0:100 Cy/EtOAc) to obtain 0.023 g of the title compound.

HPLC-MS (Method 13): R_f =2.98 min

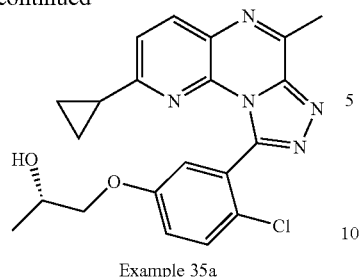
MS: m/z =384 (M+H)⁺

Example 35a



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-continued



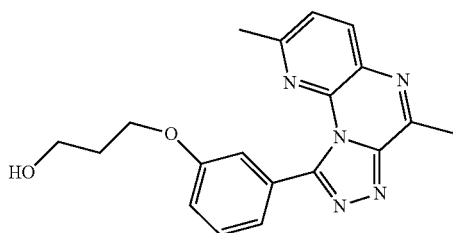
To a suspension of Intermediate 9a (0.08 g, 0.23 mmol) in dry DMF (4 mL), t-BuOK (0.076 g, 0.68 mmol) and Intermediate 21 (0.09 g, 0.45 mmol) were added and the reaction mixture was heated at 90° C. for 5 h. Dry DMF was then added and mixture heated at 110° C. overnight. Solvent was evaporated under reduced pressure, the residue dissolved in DCM and treated with a 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by flash chromatography (eluent from 80:20 to 0:100 Cy/EtOAc) to obtain 0.055 g of the protected intermediate 1-{2-chloro-5-[(S)-2-(tetrahydro-pyran-2-yloxy)-propoxy]-phenyl}-8-cyclopropyl-4-methyl-2,3,5,9,9b-pentaaza-cyclopenta[a]naphthalene.

The compound (0.055 g, 0.11 mmol) was then dissolved in dry MeOH (1 mL) and p-toluenesulfonic acid monohydrate (0.012 g, 0.06 mmol) was added. Mixture was stirred at room temperature for 1 h, solvent evaporated under reduced pressure and the residue purified by reverse phase flash chromatography (eluent ACN/H₂O from 10:100 to 100:0) and then by silica flash chromatography (eluent DCM/EtOH 90:10) to obtain 0.03 g of the title compound.

HPLC-MS (Method 9): R_f=2.69 min

MS: m/z=384 (M+H)⁺

Example 36



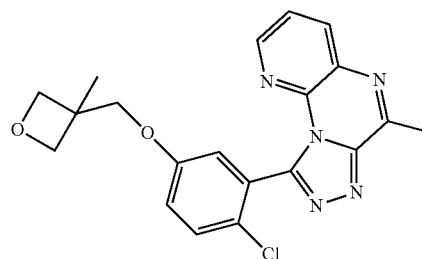
To a solution of Example 3 (0.07 g, 0.24 mmol) in dry DMF (3 mL), cesium carbonate (0.23 g, 0.71 mmol) and commercially available 3-chloro-1-propanol (0.024 g, 0.26 mmol) were added and the mixture heated at 100° C. for 3 h. Solvent was evaporated under reduced pressure, the residue dissolved with DCM and washed with 1N solution of NaOH. Phases were separated, dried over sodium sulphate and the crude purified by prep-HPLC (Method 11). Fractions containing the pure compound were combined and evaporated to reduced volume, diluted with DCM and washed with a saturated solution of sodium carbonate. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.02 g of the title compound.

HPLC-MS (Method 13): R_f=2.71 min

MS: m/z=350 (M+H)⁺

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Example 37

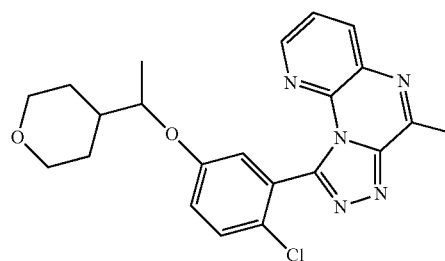


Example 37 was prepared as described for Example 32 starting from Example 1 (0.07 g, 0.22 mmol) and Intermediate 26 (0.22 g, 0.67 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.046 g of the title compound.

HPLC-MS (Method 13): R_f=3.15 min

MS: m/z=396 (M+H)⁺

Example 38

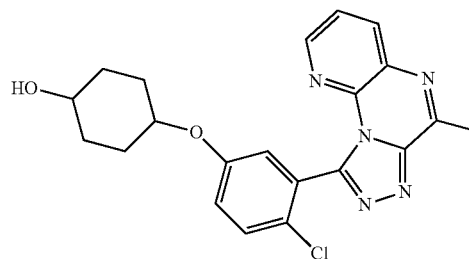


Example 38 was prepared as described for Example 32 starting from Example 1 (0.07 g, 0.22 mmol) and Intermediate 27 (0.127 g, 0.44 mmol). The residue was purified by flash chromatography (eluent from 100:0 to 50:50 Cy/EtOAc) to obtain 0.045 g of the title compound.

HPLC-MS (Method 13): R_f=3.45 min

MS: m/z=424 (M+H)⁺

Example 39



To a solution of Intermediate 30 (0.18 g, 0.44 mmol) in absolute EtOH (10 mL) sodiumborohydride (0.008 g, 0.22 mmol) was added and the mixture stirred at room temperature for 30 min. Solvent was evaporated under reduced pressure, the residue treated with DCM and washed with a saturated

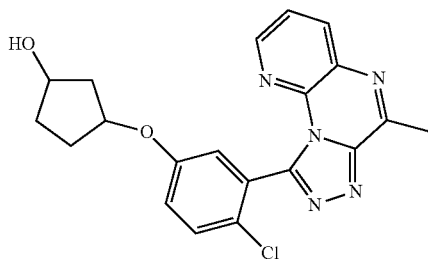
139

solution of sodium carbonate. Phases were separated, dried over sodium sulphate and evaporated under reduced pressure to obtain 0.047 g of the title compound.

HPLC-MS (Method 13): $R_f=2.96$ min

MS: $m/z=410$ (M+H)⁺

Example 40

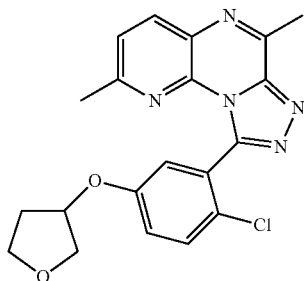


Example 40 was prepared as described Example 14, starting from Example 1 (0.075 g, 0.24 mmol) and Intermediate 31 (0.12 g, 0.48 mmol). Crude was purified by flash chromatography (eluent from 100:0 to 95:5 DCM/EtOH) to obtain 0.046 g of the title compound.

HPLC-MS (Method 13): $R_f=2.87$ min

MS: $m/z=396$ (M+H)⁺

Example 41

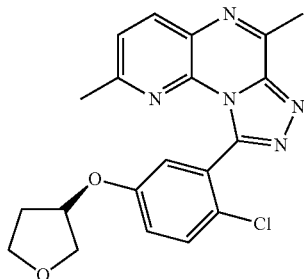


Example 41 (0.05 g) was prepared as described for Example 22 and purified applying the most suitable purification technique, starting from Example 2 (0.1 g, 0.3 mmol).

HPLC-MS (Method 13): $R_f=3.21$ min

MS: $m/z=396$ (M+H)⁺

Example 42



Example 42 (0.06 g) was prepared as described for Example 23 and purified applying the most suitable purification technique, starting from Example 2 (0.09 g, 0.28 mmol).

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(HPLC-MS (Method 13): $R_f=3.21$ min

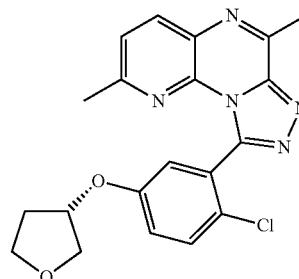
MS: $m/z=396$ (M+H)⁺

Example 43

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Example 43 (0.03 g) was prepared as described for Example 24 and purified applying the most suitable purification technique, starting from Example 2 (0.09 g, 0.28 mmol).

HPLC-MS (Method 13): $R_f=3.21$ min

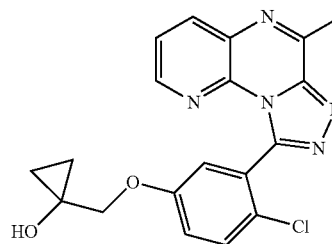
MS: $m/z=396$ (M+H)⁺

Example 43a

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To a solution of ethylmagnesium bromide (0.7 mL of a 3M solution in diethyl ether) in dry DCM (2 mL) at -75°C ., titanium(IV) isopropoxide (0.2 mL, 0.7 mmol) was added. Mixture was stirred for 10 min, then a solution of Intermediate 31 (0.28 g, 0.73 mmol) in dry DCM (8 mL) was added dropwise. Mixture was allowed to reach room temperature and stirred at room temperature overnight. Mixture was diluted with EtOAc, hydrochloric acid (1 N solution) was added and phases separated. Organics were dried over sodium sulphate and evaporated under reduced pressure and the crude purified by silica flash chromatography (eluent AcOEt/EtOH 90:10) followed by a reverse phase chromatography to obtain 0.006 g of the title compound.

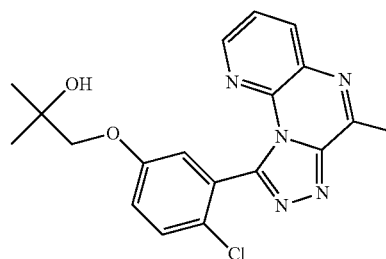
HPLC-MS (Method 13): $R_f=2.93$ min

MS: $m/z=382$ (M+H)⁺

Example 44

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Example 1 (0.07 mg, 0.2 mmol) was dissolved in DMF (3 mL), isobutylene oxide (0.03 mg, 0.43 mmol) and cesium carbonate (208 mg, 0.64 mmol) were added and the reaction mixture was warmed to 100° C. for 2 h. The solvent was removed, dichloromethane was added and the organic phase was washed with a 1M NaOH water solution, dried over sodium sulfate, concentrated under vacuum. The crude prod-


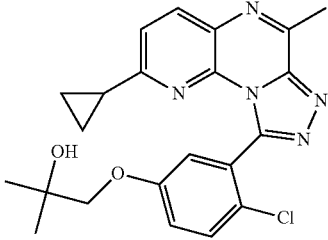

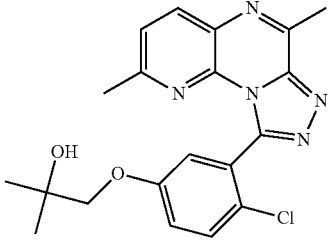

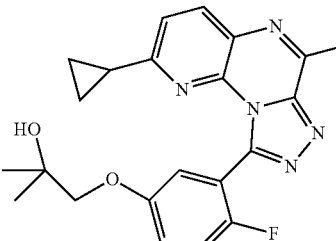

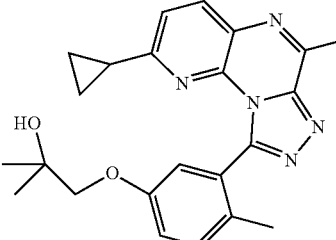
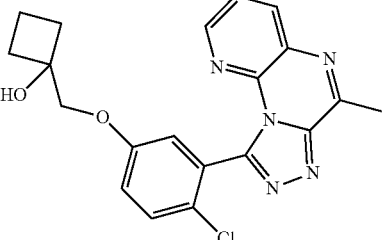
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uct obtained was purified by reverse phase chromatography to give the desired compound (29 mg).

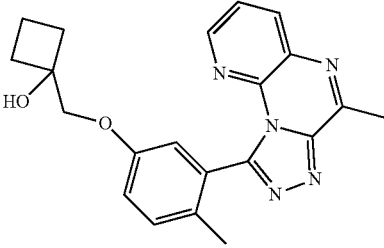

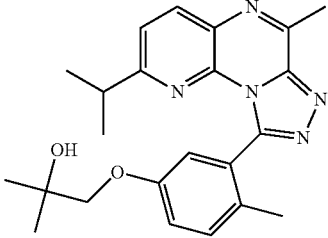

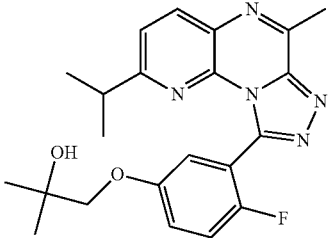
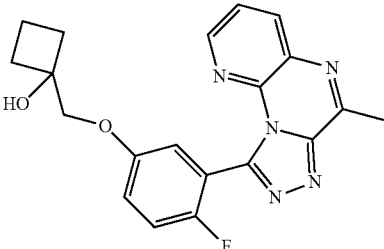

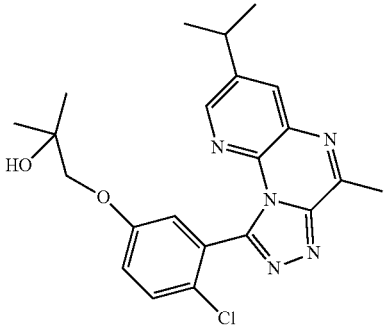
HPLC-MS (Method 13): R_f =2.93 min

MS: m/z =386 (M+H)⁺


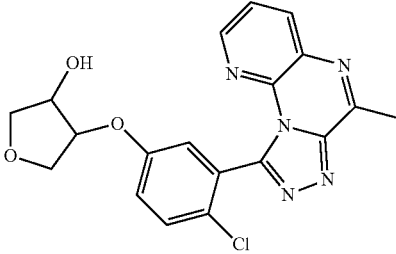
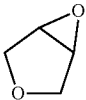
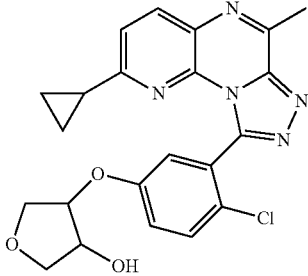
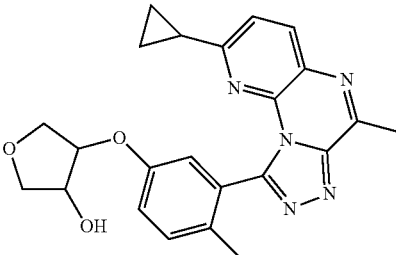
The following Examples were prepared in analogy to Example 44 and purified applying the most suitable purification technique, starting from the corresponding Starting Example and the suitable epoxides.

Starting Example of Starting Intermediate	Starting Epoxide	Ex. #	Structure	MS m/z [M + H] ⁺	R_f (min)	Method
9		45		424	2.88	9
2		46		398	3.01	9
5		47		408	3.19	13
6		48		404	3.19	13
1	29a	49		396	3.04	13

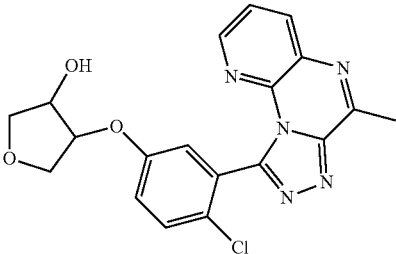
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Starting Example of Starting Intermediate	Starting Epoxide	Ex. #	Structure	MS m/z [M + H] ⁺	R _t (min)	Method
10	29a	50		376	2.88	13
7		51		406	3.32	13
8		52		410	3.32	13
4	29a	53		380	2.89	13
30p		54		426	3.56	13

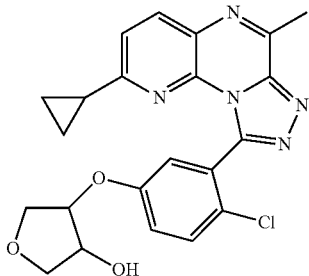
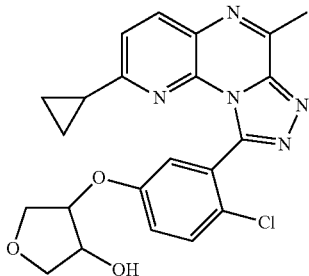
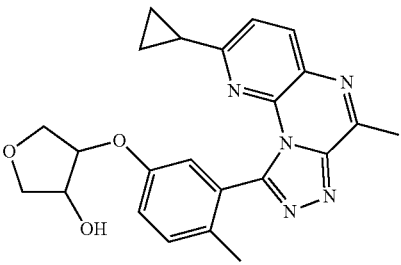
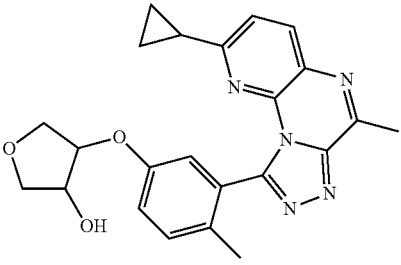
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Starting Example of Starting Intermediate	Starting Epoxide	Ex. #	Structure	MS m/z [M + H] ⁺	R _f (min)	Method
1		55 TRANS- racemic mixture		398	2.74	13
9		56 TRANS- racemic mixture		438	3.10	13
6		57 TRANS- racemic mixture		418	2.94	13

The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding racemic mixture. 50

Starting Racemic Mixture	Ex. #	Structure	MS m/z [M + H] ⁺	R _f (min) [LC-MS Method]	R _f (min) [Chiral HPLC Method]
55 TRANS- racemic mixture	55a TRANS- single stereoisomer a		398	2.63 [13]	8.23 [C1]

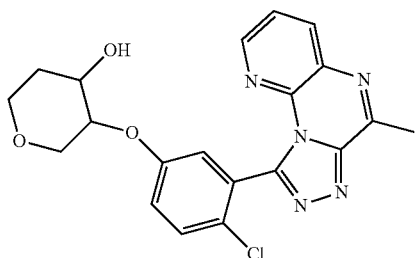
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Starting			MS	R _f (min)	R _f (min)
Racemic			m/z	[LC-MS	[Chiral HPLC
Mixture	Ex. #	Structure	[M + H] ⁺	Method]	Method]
56 TRANS- racemic mixture	56a TRANS- single stereoisomer a		438	3.03 [13]	12.13 [C2]
56 TRANS- racemic mixture	56b TRANS- single stereoisomer b		438	3.03 [13]	16.56 [C2]
57 TRANS- racemic mixture	57a TRANS- single stereoisomer a		418	2.18 [13]	17.66 [C2]
57 TRANS- racemic mixture	57b TRANS- single stereoisomer b		418	2.81 [13]	19.81 [C2]

149

Example 58

TRANS-single Stereoisomer a



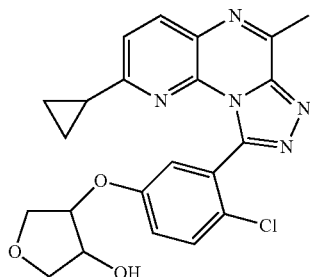
Example 58 (0.01 g) was prepared in analogy to example 44 starting from Example 1 (0.2 g, 0.61 mmol) and epoxide intermediate 29 (0.07 g, 0.73 mmol) after chiral HPLC separation HPLC-MS (Method 13): R_f =2.63 min

MS: m/z =412 (M+H)⁺

Chiral HPLC (Method C2): R_f =16.84 min

Example 58a

CIS-racemic Mixture



To a solution of Intermediate 30o (0.13 g, 0.37 mmol) in dry DMF (3 mL), potassium tert.butoxide (0.083 g, 0.73 mmol) and commercially available 1,4-anhydroerythritol (0.06 mL, 0.73 mmol) were added and mixture heated at 90 °C for 6 h. Solvent was evaporated, DCM and water added. Organics were separated, washed with a saturated solution of ammonium chloride, evaporated. The crude was purified by flash chromatography (eluent Cy/EtOAc 90:10 to 0:100) to give the desired compound (0.055 g).

HPLC-MS (Method 13): R_f =2.94 min

MS: m/z =438 (M+H)⁺

150

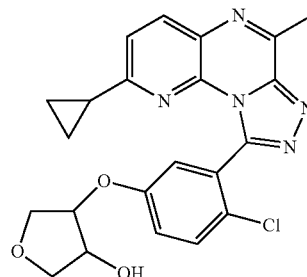
Example 58b

CIS-single Stereoisomer a

5

10

15



20

Example 58b was obtained by chiral HPLC separation of Example 58.

HPLC-MS (Method 13): R_f =2.95 min

MS: m/z =438 (M+H)⁺

25

Chiral HPLC (Method C1): R_f =7.65 min

Example 58c

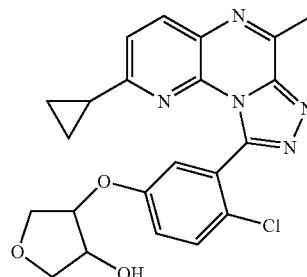
30

CIS-single Stereoisomer b

35

40

45



Further elution from the chiral column in the purification of Example 58 gave Example 58c

HPLC-MS (Method 13): R_f =2.95 min

50

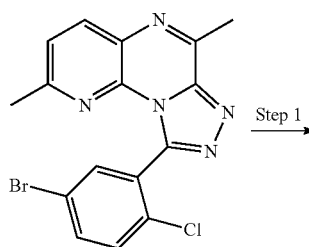
MS: m/z =438 (M+H)⁺

Chiral HPLC (Method C1): R_f =9.54 min

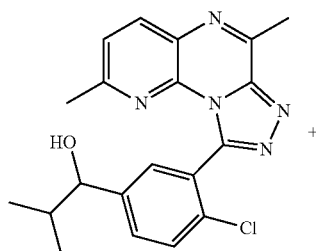
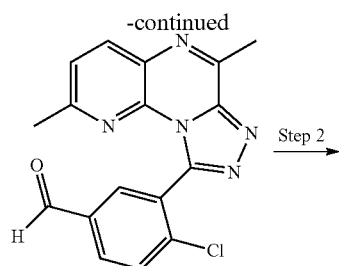
Example 59 and Example 60

60

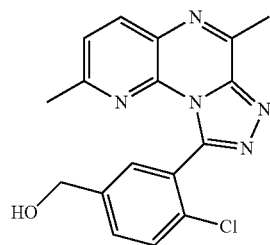
65



151



Example 59



Example 60

Step 1:

Scaffold Intermediate 30a (1.4 g, 3.5 mmol) was suspended in THF (40 mL) and stirred at -78°C . under nitrogen

152

atmosphere. N-Butyllithium (3 mL of a 2.5M solution in hexane) was added dropwise and the reaction mixture was stirred at -78°C . for 0.5 h. A solution of N,N-dimethylformamide (1.43 mL, 17.6 mmol) in THF (15 mL) was added dropwise and the reaction mixture was stirred at -78°C . for 30 minutes. Ammonium chloride saturated water solution (20 mL) was added and the reaction mixture was allowed to reach room temperature. The reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 80:20 Cy/EtOAc) to obtain the title compound (0.3 g).

Step 2:

Intermediate obtained from Step 1 (0.07 g, 0.21 mmol) was suspended in THF (2 mL) and stirred at 0°C . A 2M solution of isopropylmagnesium chloride in THF (0.1 mL) was added and the reaction mixture was allowed to reach room temperature in 2 h. Ammonium chloride saturated water solution (20 mL) was added and the reaction mixture was allowed to reach room temperature. The reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (eluent 50:50 Cy/EtOAc) to obtain Example 60 (0.02 g).

HPLC-MS (Method 9): $R_t=2.85$ min

MS: $m/z=382$ ($M+H$)⁺

Further elution from the column (eluent from 50:50 to 0:100 Cy/EtOAc) gave Example 60 (0.03 g)

HPLC-MS (Method 9): $R_t=2.28$ min

MS: $m/z=340$ ($M+H$)⁺

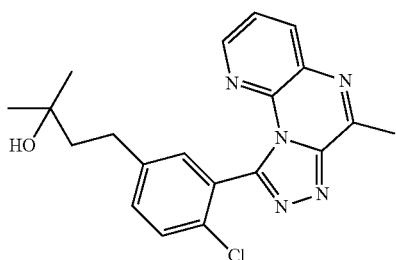
The following examples were prepared in analogy to Example 59 and purified applying the most suitable purification technique, starting from Scaffold Intermediate 30a and the corresponding commercially available Grignard reagents.

Grignard reagent	Ex. #	Structure	MS m/z ($M+H$) ⁺	R_t (min)	Method
	61		382	2.89	9
	62		368	3.12	13

-continued

Grignard reagent	Ex. #	Structure	MS m/z (M + H) ⁺	R _t (min)	Method
—Mg—Cl	63		354	2.93	13

Example 64

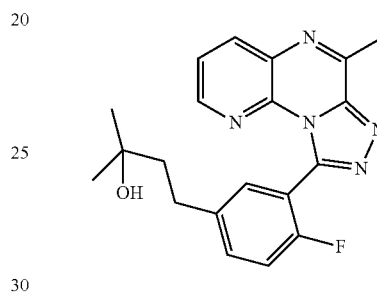


Example 64 (0.03 g) was prepared in analogy to Example 1 and purified applying the most suitable purification technique, starting from Intermediate 2 (0.1 g, 0.55 mmol) and Hydrazide Intermediate 6i (0.15 g, 0.55 mmol).

HPLC-MS (Method 9): R_t=2.52 min

MS: m/z=382 (M+H)⁺

Example 65



Example 65 (0.03 mg) was prepared in analogy to the preparation of Intermediate 5i and purified applying the most suitable purification technique, starting from Scaffold Intermediate 30d (0.1 g, 0.25 mmol).

HPLC-MS (Method 9): R_t=2.45 min

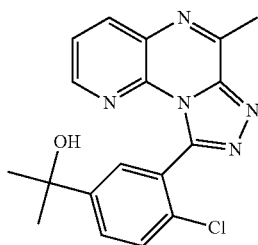
MS: m/z=366 (M+H)⁺

The following examples were prepared in analogy to Example 65 and purified applying the most suitable purification technique, starting from the corresponding Scaffold Intermediates.

Starting Intermediate	Ex. #	Structure	MS m/z (M + H) ⁺	R _t (min)	Method
30e	66		406	3.29	13
30f	67		362	3.83	16

Starting Intermediate	Ex. #	Structure	MS m/z (M + H) ⁺	R _t (min)	Method
30g	68		402	3.22	13
30h	69		422	3.33	13

Example 70



Example 70 (0.03 g) was prepared in analogy to the preparation of Intermediate 5j and purified applying the most suitable purification technique, starting from Scaffold Intermediate 30b (0.16 g, 0.38 mmol) and acetone (0.07 mg, 1.13 mmol).

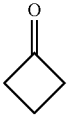
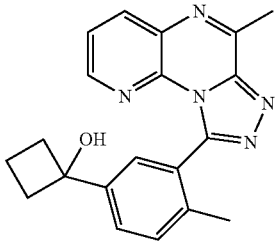
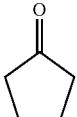
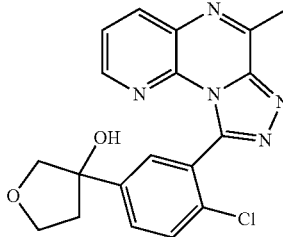
HPLC-MS (Method 13): R_t=2.67 min

MS: m/z=354 (M+H)⁺

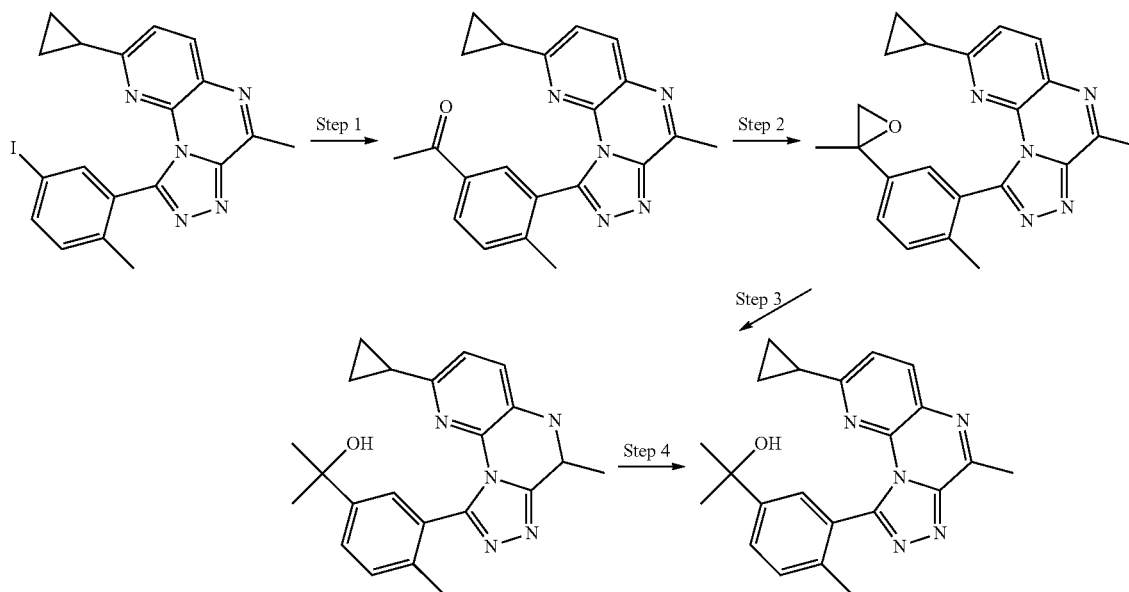
The following examples were prepared in analogy to Example 70 and purified applying the most suitable purification technique, starting from the corresponding Scaffold Intermediates and commercially available ketons.

Starting Intermediate	Ketone	Ex. #	Structure	MS m/z (M + H) ⁺	R _t (min)	Method
30j		71		368	2.95	13
30m		72		392	3.32	13

-continued

Starting Intermediate	Ketone	Ex. #	Structure	MS m/z (M + H) ⁺	R _f (min)	Method
30c		73		346	2.77	13
30b		74		382	2.61	13

Example 75



Step 1:

Under N₂ atmosphere, to a solution of Scaffold Intermediate 30 g (1.0 g, 2.54 mmol) in toluene (35 mL), tributyl-(1-ethoxyvinyl)-tin (1.3 mL, 3.04 mmol) and Pd tetrakis(triphenylphosphine) (580 mg, 0.51 mmol). The solution was stirred at 105° C. for 18 h. The reaction mixture was cooled at room temperature, concentrated in vacuo and the crude product obtained was dissolved in THF. A 2N water solution of HCl 2N (5 ml) was added and the reaction mixture was stirred for 30 mins. After dilution with ethyl acetate, phases were separated and organic layer was dried over sodium sulfate and concentrated. The crude product obtained was purified by flash chromatography (eluent from 90:10 to 75:25 Cy/EtOAc) to obtain the desired compound (0.8 g).

HPLC-MS (Method 13): R_f=3.09 min
MS: m/z=358 (M+H)⁺

Step 2:

To a solution of the intermediate from Step 1 (0.8 g, 2.2 mmol) in DCM (20 mL) 50% NaOH/H₂O solution (0.8 mL) was added and the reaction mixture was stirred for 10 minutes. Trimethylsulfonium methyl sulfate (0.4 g, 2.8 mmol) was added and the reaction mixture was refluxed for 2 h. The reaction mixture was diluted with DCM and washed with water. The organic layer was separated, dried over sodium sulfate and concentrated. The crude product obtained was purified by flash chromatography (eluent 85:15 Cy/EtOAc) to obtain the desired compound (0.5 g).

HPLC-MS (Method 13): R_f=3.33 min
MS: m/z=372 (M+H)⁺

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Step 3:

To a solution of lithiumaluminumhydride (0.15 mL of a 2M solution in THF) in 15 mL of THF stirred at 0° C., the intermediate from step 2 (0.4 g, 0.4 mmol) was added slowly. The reaction mixture was stirred for 1 h and allowed to reach room temperature. Water (2 mL) and NaOH (1 mL of a 2M water solution) were added and the reaction mixture was diluted with ethyl acetate. Organic phase was separated, dried over sodium sulfate and concentrated to give the desired product (0.28 g).

HPLC-MS (Method 13): R_f =3.0 min

MS: m/z =376 (M+H)⁺

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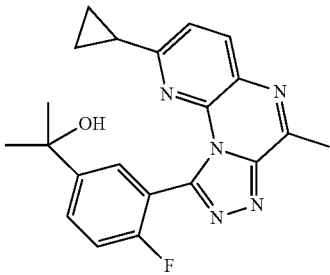
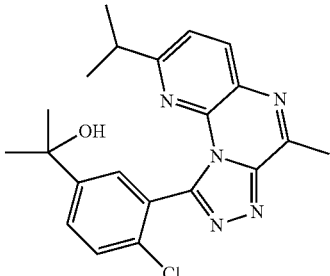
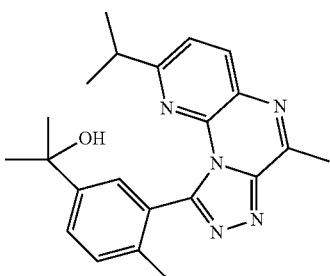
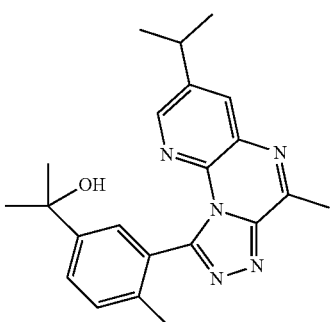
Step 4:

Intermediate from step 3 (0.17 g, 0.38 mmol) was dissolved in DCM (10 mL), manganese dioxide (0.38 g, 3.38 mmol) was added and the suspension was stirred for 1 h at room temperature. The reaction mixture was filtered on a celite pad and the solvent was evaporated. The crude product obtained was purified by flash chromatography (eluent 90:10 DCM/MeOH) to obtain the desired compound (0.14 g).

HPLC-MS (Method 13): R_f =3.04 min

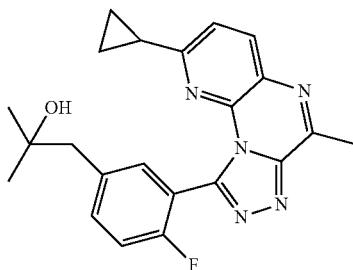
MS: m/z =374 (M+H)⁺

The following examples were prepared in analogy to Example 75 and purified applying the most suitable purification technique, starting from the corresponding Intermediates.

Starting Intermediate	Ex.	Structure	MS m/z (M + H) ⁺	R_f (min)	Method
30e	76		378	3.12	13
30k	77		396	3.37	13
30l	78		376	3.3	13
30n	79		376	3.31	13

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Example 80



Example 80 (0.02 g) was prepared in step 2, step 3 and step 4 step in analogy to Example 75 and purified applying the most suitable purification technique, starting from the Intermediate obtained in step 1.

Step 1 was performed as follow:

Scaffold Intermediate 30i (1.35 g, 3.39 mmol) tri-n-butylmethoxytin (1.51 mL, 5.08 mmol), isopropenyl acetate (5.6

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mL, 51 mmol), tri-o-tolylphosphine (0.07 g, 0.25 mmol) and palladium acetate (0.03 g) were suspended in toluene (30 mL) under nitrogen atmosphere and stirred for 2 h at room temperature, then at 110° C. for 20 minutes. Water (10 mL) and a bicarbonate saturated water solution (3 mL) were added, toluene was removed under vacuum and DCM was added. The organic phase was separated, and concentrated. The crude product obtained was purified by flash chromatography (eluent from 30:70 to 0:100 cyclohexane/AcOEt) to obtain the desired compound (0.5 g).

Step 2, Step 3 and Step 4 were performed in analogy to Example 75.

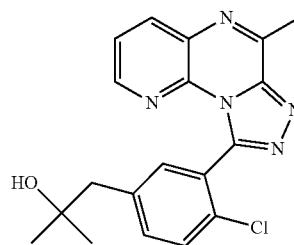
HPLC-MS (Method 16): R_f =3.13 min

MS: m/z =392 (M+H)⁺

The following example was prepared in analogy to Example 80 and purified applying the most suitable purification technique, starting from the corresponding Scaffold Intermediates.

Intermediate	Ex. #	Structure	MS m/z (M + H) ⁺	R_f (min)	Method
30g	81		388	5.75	17

Example 82



Example 82 (0.09 g) was prepared in analogy to Example 1 starting from Chloride Intermediate 2 (0.1 g, 0.61 mmol) and Hydrazide Intermediate 6p (0.2 g, 0.61 mmol).

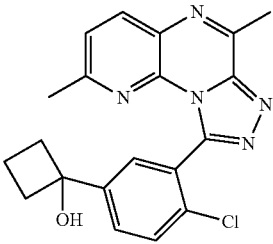
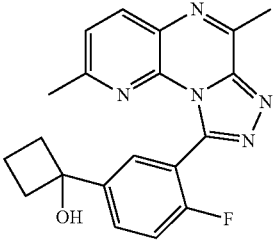
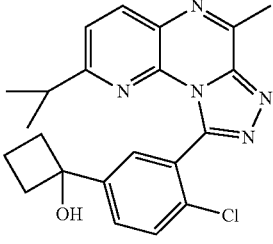
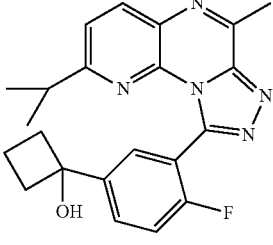
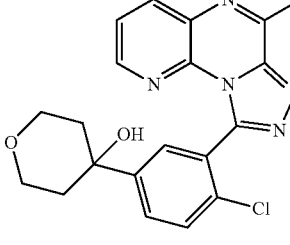
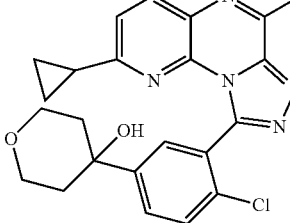
(HPLC-MS (Method 13): R_f 2.80=min

MS: m/z =368 (M+H)⁺

The following examples were prepared in analogy to Example 82 and purified applying the most suitable purification technique, starting from the corresponding Chloride and Hydrazide Intermediates.

Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex. #	Structure	MS m/z (M + H) ⁺	R _f (min)	Method
9a	6p	83		408	3.24	13
9a	6j	84		390	3.18	13
9a	6o	85		394	3.22	13
2	6j	86		350	2.76	13
2	6k	87		366	2.93	13
9a	6k	88		406	3.33	13

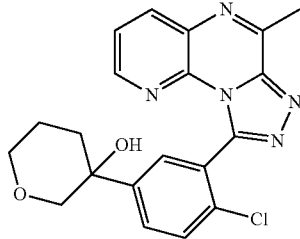
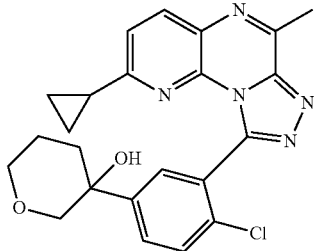
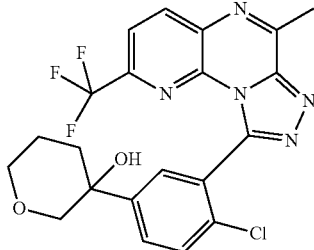
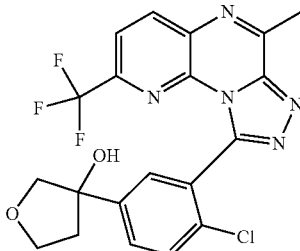
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Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex. #	Structure	MS m/z (M + H) ⁺	R _t (min)	Method
9	6k	89		380	3.05	13
9	6j	90		364	2.91	13
9b	6k	91		408	3.45	13
9b	6j	92		392	3.34	13
2	6l	93		396	2.96	13
9a	6l	94		436	3.08	13

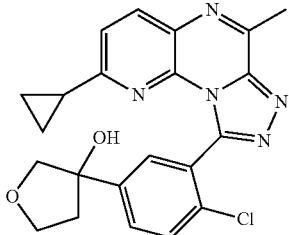
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Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex. #	Structure	MS m/z (M + H) ⁺	R _f (min)	Method
9a	6n	95		420	2.9	13
9f	6l	96		464	3.04	13
9f	6n	96a		448	2.98	13
9f	6na	96b		444	2.94	13
9f	6r	96c		434	2.91	13
9a	6q	97		422	2.90	13

-continued

Starting Chloride Intermediate	Starting Hydrazide Intermediate	Ex. #	Structure	MS m/z (M + H) ⁺	R _f (min)	Method
2	6s	112		396	2.67	13
9a	6s	113		436	3.10	13
9f	6s	114		464	3.21	13
9f	6r	115		450	3.90	13

The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding racemic mixture.

Starting Racemic Mixture	Ex. #	Structure	MS m/z [M + H] ⁺	R _f (min) [LC-MS Method]	R _f (min) [Chiral HPLC Method]
97 Racemic mixture	97a Single stereo- isomer b		422	2.89 [13]	15.75 [C2a]

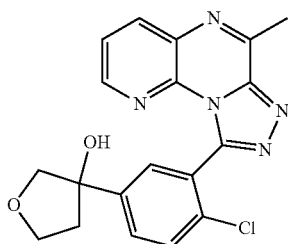
-continued

Starting Racemic Mixture	Ex. #	Structure	MS m/z [M + H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
97 Racemic mixture	97b Single stereo- isomer a		422	2.89 [13]	13.32 [C2a]
112 Racemic mixture	112a Single stereo- isomer a		396	2.85 [13]	14.5 [C2a]
112 Racemic mixture	112b Single stereo- isomer b		396	2.85 [13]	15.6 [C2a]
114 Racemic mixture	114a Single stereo- isomer a		464	3.21 [13]	13.8 [C2]
114 Racemic mixture	114b Single stereo- isomer b		464	3.21 [13]	16.76 [C2]

Starting Racemic Mixture	Ex. #	Structure	MS m/z [M + H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
115 Racemic mixture	115a Single stereo- isomer a		450	3.05 [13]	28.0 [C2b]
115 Racemic mixture	115b Single stereo- isomer b		450	3.05 [13]	31.2 [C2b]

Example 98

Single Stereoisomer a



Example 98 (0.026 g) was prepared in analogy to Example 1 starting from Chloride Intermediate 2 (0.3 g, 1.45 mmol) and Hydrazide Intermediate 6q (0.4 g, 1.56 mmol) after semi-preparative chiral purification.

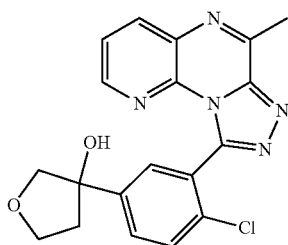
HPLC-MS (Method 13): R_t=2.56 min

MS: m/z=382 (M+H)⁺

Chiral HPLC (Method C1a): R_t=9.55 min

Example 99

Single Stereoisomer b



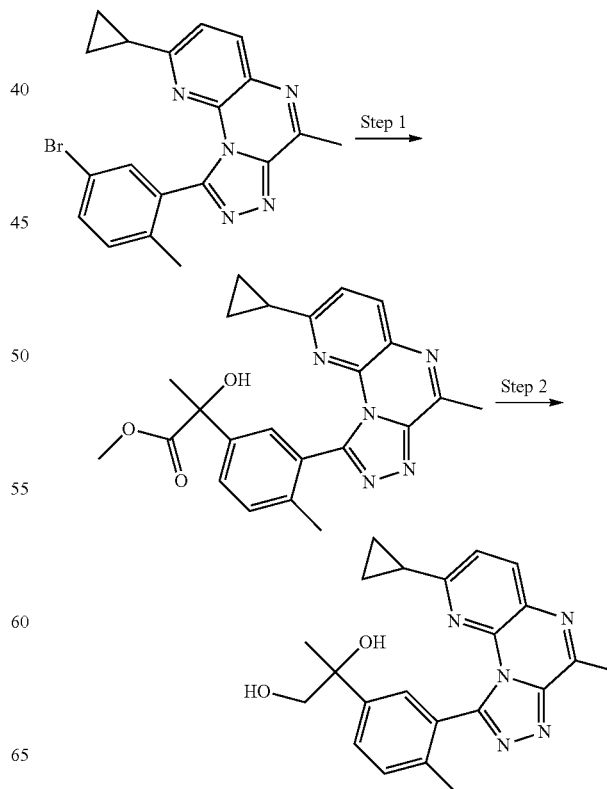
Example 99 (0.028 g) was obtained via further elution from the column in the semipreparative chiral chromatographic purification of Example 98.

HPLC-MS (Method 13): R_t=2.52 min

MS: m/z=382 (M+H)⁺

Chiral HPLC (Method C1a): R_t=11.03 min

Example 100



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Step 1:

Scaffold Intermediate 30 g (0.5 g, 1.27 mmol), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (1.9 g, 11.4 mmol), bis(dibenzylideneacetone)palladium(0) (0.14 g, 0.25 mmol) and zinc fluoride (0.19 g, 1.9 mmol) were suspended in DMF (25 mL) and stirred under nitrogen atmosphere for 10 minutes. Tri-tert-butyl-phosphine (0.06 mL, 0.25 mmol) was added and the reaction mixture was stirred at 115° C. for 18 h. The reaction mixture was concentrated, an ammonium chloride water saturated solution was added and the reaction mixture was extracted with DCM. The organic phase was separated, dried over sodium sulfate and concentrated. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 50:50 cyclohexane/AcOEt) to obtain the desired compound (0.4 g).

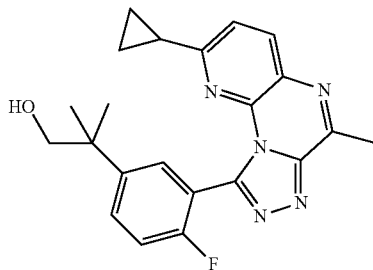
Step 2:

The intermediate obtained in Step 1 (0.4 g, 0.07 mmol) was dissolved in THF (6 mL) and stirred under nitrogen atmosphere at 0° C. for 5 minutes. Lithiumaluminium hydride (0.5 mL of a 2M solution in THF) was added. The reaction mixture was stirred at 0° C. for 10 minutes then allowed to reach room temperature and stirred for 0.5 h. The solvent was removed, the crude product was dissolved in DCM and the reaction mixture was washed with water (4 mL), bicarbonate saturated water solution (2 mL) and brine (2 mL). The organic phase was separated, dried over sodium sulfate and manganese dioxide (0.15 g, 1.73 mmol) was added. The reaction mixture was stirred for 0.5 h, filtered on a celite pad and concentrated. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 95:5 DCM/MeOH) to obtain the desired compound (0.1 g).

(HPLC-MS (Method 13): R_f =3.29 min

MS: m/z =388 (M+H)⁺

Example 101

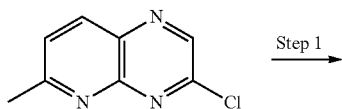


Example 101 (0.05 g) was prepared in analogy to Example 100 and purified applying the most suitable purification technique, starting from Scaffold Intermediate 30i (0.36 g, 0.9 mmol).

HPLC-MS (Method): R_f =3.3 min

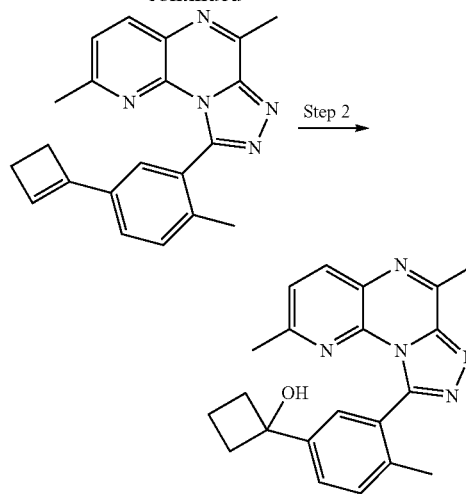
MS: m/z =392 (M+H)⁺

Example 102



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-continued



Step 1:

Step 1 was performed in analogy to preparation of Example 1 starting from Chloride Intermediate 9 (0.3 g, 1.39 mmol) and Hydrazide Intermediate 6o (0.47 g, 1.39 mmol).

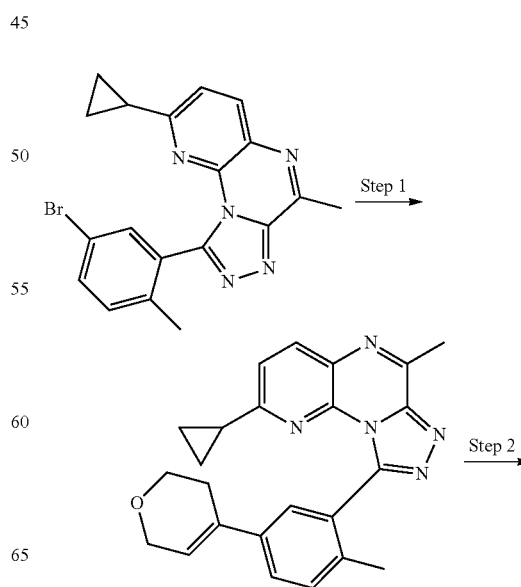
Step 2:

Intermediate from step 1 (0.09 g, 0.26 mmol) and hydrochloric acid (10 mL of a 37% water solution) were dissolved in 10 mL of 1,4-dioxane. The reaction mixture was stirred at room temperature for 20 minutes. A bicarbonate saturated water solution was added, THF was removed in vacuum and the reaction mixture was extracted with DCM. The organic phase was separated, dried over sodium sulfate and concentrated. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 90:10 DCM/MeOH) to obtain the title compound (0.03 g).

HPLC-MS (Method 13): R_f =2.95 min

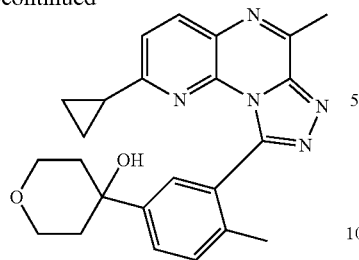
MS: m/z =360 (M+H)⁺

Example 103



177

-continued



Step 1:

Under nitrogen atmosphere, Scaffold Intermediate 30 g (0.3 g, 0.61 mmol), potassium carbonate (0.34 g, 2.4 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.05 g) were suspended in toluene (150 mL) and stirred at room temperature for 10 minutes. 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (0.17 g, 0.79 mmol) was added and the reaction mixture was stirred at 100° C. for 4 h. Water (30 mL) was added and the reaction mixture was extracted with AcOEt. The organic phase was separated and concentrated. The crude product obtained was purified by flash chromatography (eluent from 100:0 to 90:10 DCM/MeOH) to obtain the title compound (0.02 g).

Step 2:

Step 2 was performed in analogy to Step 2 in the preparation of Example 102.

0.02 g of the desired product were obtained after purification by flash chromatography (eluent from 100:0 to 90:10 DCM/MeOH).

(HPLC-MS (Method 13): R_t =2.88 min

MS: m/z =416 (M+H)⁺

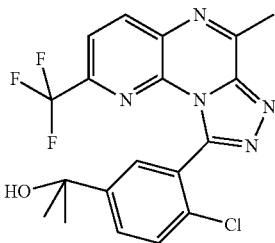
The following examples were prepared in analogy to Example 103 and purified applying the most suitable purification technique, starting from the corresponding Scaffold Intermediate and the boronic ester 2-Isopropenyl-4,4,5,5-tetramethyl-1,3,2]dioxaborolane.

Start-
ing
Inter-
medi-
ateEx.
#

Structure

MS
 m/z
(M +
H)⁺ R_t
(min)Meth-
od

30r 103b

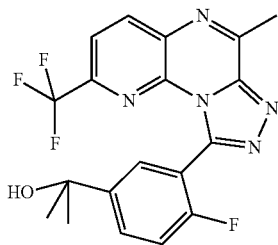


422

3.25

13

30s 103c



406

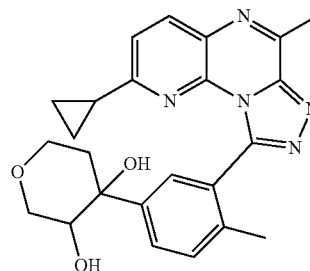
3.17

13

178

Example 104

CIS-racemic Mixture



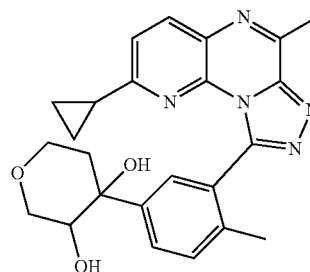
Intermediate obtained from Step 1 in preparation of Example 103 (50 mg, 0.13 mmol) was dissolved in DCM (5 mL). Osmium tetroxide (0.1 mL, 0.01 mmol) and 4-methylmorpholine-4-oxide (0.07 g, 0.63 mmol) were added and the reaction mixture was stirred at room temperature for 5 h. The solvent was removed and the crude product obtained was purified by flash chromatography (eluent from 100:0 to 80:20 DCM/MeOH) to obtain the title compound (0.03 g).

HPLC-MS (Method 13): R_t =2.73 min

MS: m/z =432 (M+H)⁺

Example 104a

CIS-single Stereoisomer a



Example 104a was obtained via Chiral HPLC purification of Example 104.

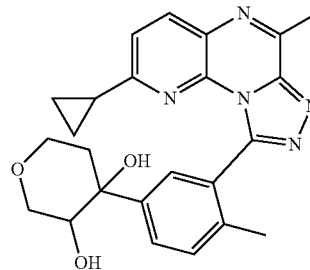
HPLC-MS (Method 13): R_t =2.65 min

MS: m/z =432 (M+H)⁺

Chiral HPLC (Method C2b): R_t =18.70 min

Example 104b

CIS-single Stereoisomer b



Further elution from the chiral column gave Example 104b.

HPLC-MS (Method 13): R_t =2.65 min

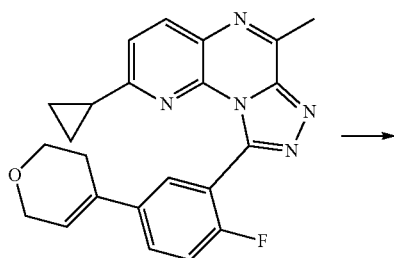
MS: m/z =432 (M+H)⁺

Chiral HPLC (Method C2b): R_t =21.04 min

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Example 105

CIS-racemic Mixture

**180**

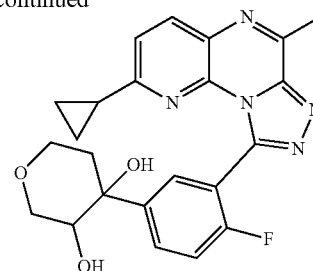
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5

10

15

20

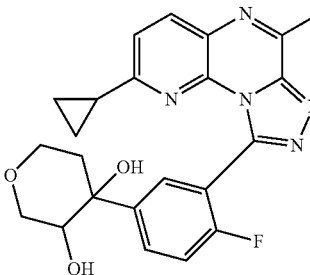
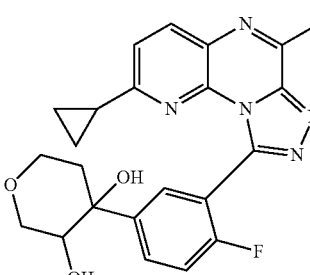


Example 105 (0.03 g) was prepared in analogy to Example 104, starting from 8-Cyclopropyl-1-[5-(3,6-dihydro-2H-pyran-4-yl)-2-fluoro-phenyl]-4-methyl-2,3,5,9,9b-pentaaza-cyclopenta[a]naphthalene (0.05 g, 0.12 mmol) which was obtained as by-product in the preparation of Example 95 and isolated from the same flash chromatography purification.


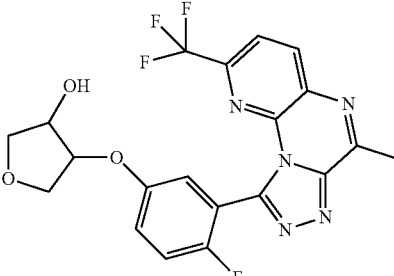

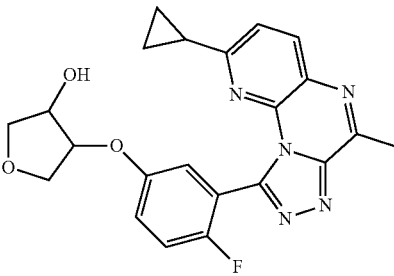

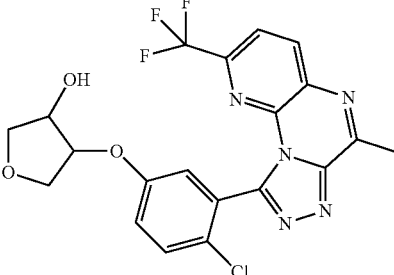
HPLC-MS (Method 13): $R_t=2.68$ min

MS: $m/z=436$ (M+H)⁺

The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding racemic mixture.

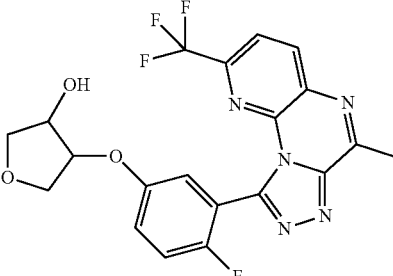
Starting Racemic Mixture	Ex. #	Structure	MS m/z [M + H] ⁺	R _t (min)	
				[LC-MS Method]	[Chiral HPLC Method]
105 CIS- Racemic mixture	105a CIS- Single stereo- isomer a		436	2.69 [13]	15.05 [C2b]
97 CIS- Racemic mixture	105b CIS- Single stereo- isomer b		436	2.68 [13]	18.47 [C2b]

The following Examples were prepared in analogy to Example 44 and purified applying the most suitable purification technique, starting from the corresponding Starting Example and the corresponding epoxides.

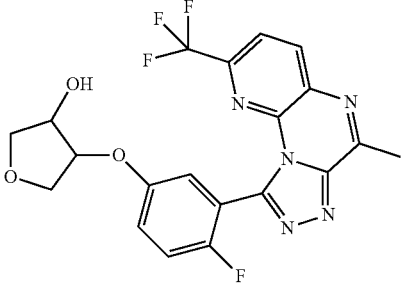
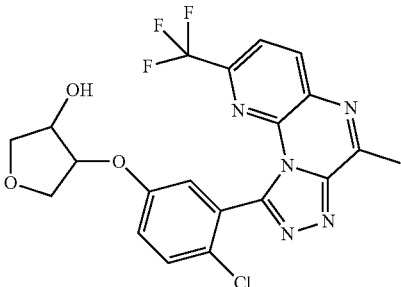
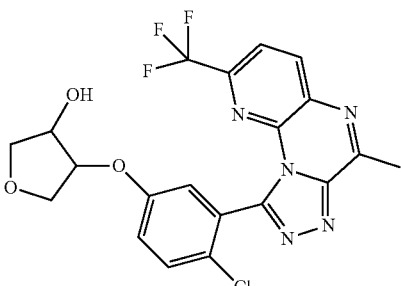
Starting Example or Starting Intermediate	Starting Epoxide	Ex. #	Structure	MS m/z (M + H) ⁺	R _t (min)	Method
Intermediate 32		106 TRANS-Racemic mixture		450	2.97	13
5		107 TRANS-Racemic mixture		422	3.88	16
12		111 TRANS-Racemic mixture		466	3.09	13

45

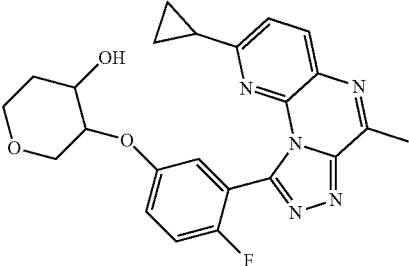
The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding racemic mixture.

Starting Racemic Mixture	Ex. #	Structure	MS m/z [M + H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
106 TRANS-Racemic mixture	106a TRANS-single stereoisomer a		450	2.95 [13]	7.77 [C2c]

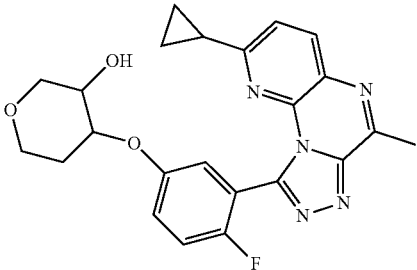
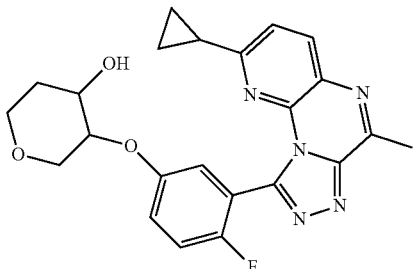
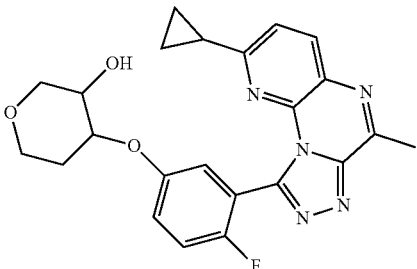
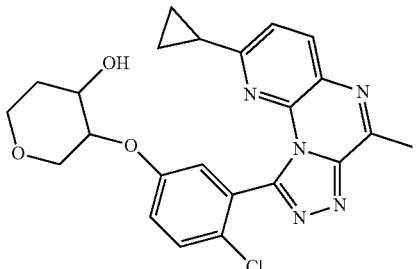
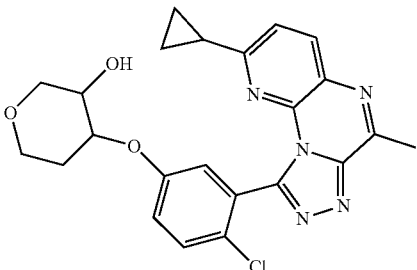
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Starting Racemic Mixture	Ex. #	Structure	MS m/z [M + H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
106 TRANS- Racemic mixture	106b TRANS- single stereo- isomer b		450	2.98 [13]	11.58 [C2c]
111 TRANS- Racemic mixture	111a TRANS- single stereo- isomer a		466	3.10 [13]	13.65 [C2]
111 TRANS- Racemic mixture	111b TRANS- single stereo- isomer b		466	3.10 [13]	16.14 [C2]

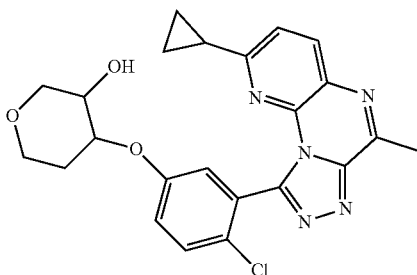
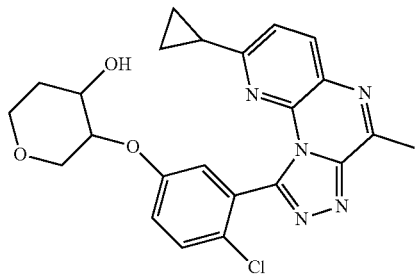
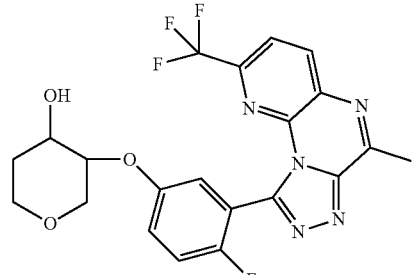
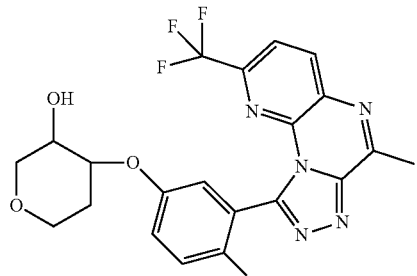
The following examples were obtained as single stereoisomers by chiral HPLC separation of the corresponding TRANS regioisomeric racemic mixtures. TRANS regioisomeric racemic mixtures were obtained in analogy to preparation of Example 44, starting from epoxide Intermediate 29 and the corresponding Starting Examples or Starting Intermediates.

Starting Example or Starting Intermediate	Ex. #	Structure	MS m/z [M + H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
5	108a TRANS- single stereo- isomer b		436	2.91 [13]	31.54 [C3]

-continued

Starting Example or Starting Intermediate	Ex. #	Structure	MS m/z [M + H] ⁺	R _f (min)	
				[Chiral LC-MS Method]	[Chiral HPLC Method]
5	108c TRANS- single stereo- isomer b		436	2.91 [13]	44.59 [C2c]
5	108b TRANS- single stereo- isomer a		436	2.92 [13]	27.61 [C3]
5	108d TRANS- single stereo- isomer a		436	2.91 [13]	22.06 [C2c]
9	109a TRANS- single stereo- isomer a		452	3.03 [13]	23.62 [C2]
9	109c TRANS- single stereo- isomer a		452	3.03 [13]	40.91 [C2]

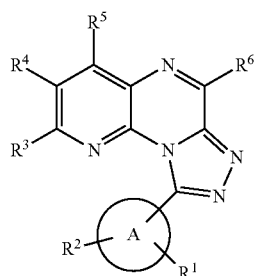
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Starting Example or Starting Intermediate	Ex. #	Structure	MS m/z [M + H] ⁺	R _t (min) [LC-MS Method]	R _t (min) [Chiral HPLC Method]
9	109b TRANS- single stereo- isomer b		452	3.03 [13]	89.29 [C2]
9	109d TRANS- single stereo- isomer b		452	3.03 [13]	25.61 [C2]
Intermediate 32	110b TRANS- single stereo- isomer b		464	3.00 [13]	21.99 [C2]
Intermediate 32	110d TRANS- single stereo- isomer b		464	3.02 [13]	62.95 [C2]

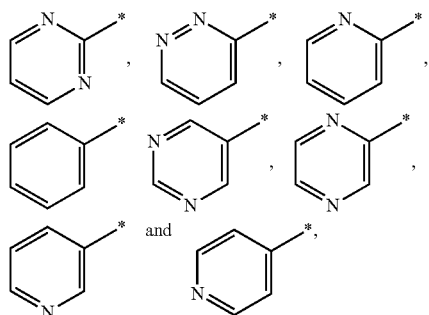
189

The invention claimed is:

1. A compound of formula I



wherein

A is selected from the group A^a consisting of

wherein the above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl- and pyrazinyl-groups are substituted with R¹ and R²;

R¹ is selected from the group R^{1a} consisting of

H, halogen, NC—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— wherein n is 0, 1, 2, 3 or 4,

wherein the above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO— and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms;

R² is selected from the group R^{2a1} consisting of

HO—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— wherein n is 0, 1, 2, 3 or 4, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— wherein m is 0, 1 or 2 and o is 0, 1 or 2

wherein the above mentioned C₁₋₆-alkyl- and C₁₋₆-alkyl-O-groups are substituted with 1 to 5 substituents independently selected from the group consisting of HO— and C₁₋₃-alkyl-O— optionally substituted with 1 to 7 fluorine atoms,

and

wherein the above mentioned C₁₋₆-alkyl- and C₁₋₆-alkyl-O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms,

and

wherein the above mentioned C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-

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C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, C₁₋₃-alkyl-O— optionally substituted with 1 to 7 fluorine atoms, and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms;

R³ is selected from the group R^{3a} consisting of

H, halogen, NC—, C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-,

wherein the above mentioned C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC—, HO—, C₁₋₃-alkyl- and C₁₋₃-alkyl-O—;

R⁴ and R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC—, HO—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O—,

wherein the above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O— groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₂-alkyl- optionally substituted with 1 to 5 halogen atoms, and C₁₋₂-alkyl-O— optionally substituted with 1 to 5 halogen atoms;

R⁶ is selected from the group R^{6a} consisting of

H, NC—, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O—

wherein the above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of

H, carbocyclyl, heterocyclyl and heteroaryl,

wherein the above mentioned carbocyclyl, heterocyclyl and heteroaryl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of HO—, C₁₋₄-alkyl- optionally substituted with 1 to 3 halogen atoms, C₁₋₄-alkyl-O— optionally substituted with 1 to 3 halogen atoms and halogen; and

R⁸ is selected from the group R^{8a} consisting of

C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl,

wherein the above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and C₁₋₃-alkyl- optionally substituted with 1 to 7 halogen atoms;

or a tautomer or pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

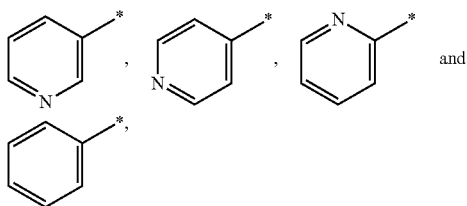
R³ is selected from the group R^{3a1} consisting of

C₃₋₆-cycloalkyl-,

wherein the above mentioned C₃₋₆-cycloalkyl-group may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC—, HO—, C₁₋₃-alkyl- and C₁₋₃-alkyl-O—.

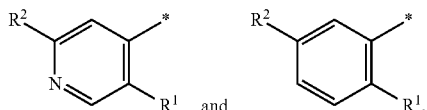
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3. A compound according to claim 1, wherein A is selected from the group A^b consisting of



wherein the above mentioned phenyl- and pyridinyl-groups are substituted with R¹ and R².

4. A compound according to claim 1, wherein A is selected from the group A^c consisting of



5. A compound according to claim 1, wherein R¹ is selected from the group R^{1b} consisting of

H, halogen, C₁₋₆-alkyl- and C₃₋₆-cycloalkyl wherein the above mentioned C₁₋₆-alkyl- and C₃₋₆-cycloalkyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO— and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms.

6. A compound according to claim 1, wherein R¹ is selected from the group R^{1c} consisting of

H, H₃C—, F₃C—, F₂HC—, FH₂C—, fluorine, chlorine and bromine.

7. A compound according to claim 1, wherein R² is selected from the group R^{2b1} consisting of

HO—, C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— with n is 0, 1, 2 or 3 and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— with m is 0 or 1 and o is 0 or 1 wherein the above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups are substituted with 1 to 3 substituents independently selected from the group consisting of HO— and C₁₋₃-alkyl-O— optionally substituted with 1 to 7 fluorine atoms,

and

wherein the above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O— groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms,

and

wherein the above mentioned C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, HO—, C₁₋₃-alkyl-O— optionally substituted with 1 to 7 fluorine atoms, and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms.

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8. A compound according to claim 1, wherein R² is selected from the group R^{2d1} consisting of

HO—, C₁₋₄-alkyl-, C₁₋₄-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, a saturated 5 or 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸—(CH₂)_n—O— with n is 0, 1 or 2, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— m is 0 or 1 and o is 0 or 1

wherein the above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups are substituted with 1 to 5 substituents independently selected from the group consisting of HO—, and C₁₋₃-alkyl-O— optionally substituted with 1 to 7 fluorine atoms,

and

wherein the above mentioned C₁₋₄-alkyl- and C₁₋₄-alkyl-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms,

and

wherein the above mentioned C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, saturated 5 or 6 membered monocyclic heterocycle containing one heteroatom selected from N or O, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, optionally substituted with 1 to 7 fluorine atoms, and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms.

9. A compound according to claim 1, wherein

R³ is selected from the group R^{3b} consisting of

H, C₁₋₃-alkyl-, cyclobutyl- and cyclopropyl-, wherein the above mentioned C₁₋₃-alkyl-, cyclobutyl- and cyclopropyl-groups may optionally be substituted with 1 to 7 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl-O—, NC— and HO—.

10. A compound according to claim 1, wherein

R³ is selected from the group R^{3c} consisting of

H, H₃C— and cyclopropyl-, wherein the above mentioned H₃C— and cyclopropyl-groups may optionally be substituted with 1 to 3 fluorine atoms.

11. A compound according to claim 1, wherein

R⁴ and R⁵ are selected independently of each other from the group R^{4b}/R^{5b} consisting of

H, halogen, HO—, H₃C—, F₃C—, H₃C—O—, F₂HC—O—, FH₂C—O—, F₃C—O—, C₁₋₄-alkyl-O—, R⁷—CH₂—O— and R⁷—(CH₂)₂—O—,

wherein the above mentioned C₁₋₄-alkyl-O—, R⁷—CH₂—O— and R⁷—(CH₂)₂—O— groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₂-alkyl- optionally substituted with 1 to 5 halogen atoms, and C₁₋₂-alkyl-O— optionally substituted with 1 to 5 halogen atoms.

12. A compound according to claim 1, wherein

R⁴ and R⁵ are selected from the group R^{4d}/R^{5d} consisting of H—.

13. A compound according to claim 1, wherein

R⁶ is selected from the group R^{6b} consisting of

H, C₁₋₄-alkyl- and cyclopropyl-, wherein the above mentioned C₁₋₄-alkyl-group may optionally be substituted with 1-3 fluorine and/or chlorine atoms.

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14. A compound according to claim 1, wherein R^6 is selected from the group R^{6c} consisting of H and C_{1-2} -alkyl-, wherein the above mentioned C_{1-2} -alkyl-group may optionally be substituted with 1-3 fluorine and/or chlorine atoms. 5

15. A compound according to claim 1, wherein R^6 is selected from the group R^{6e} consisting of H_3C- , FH_2C- , F_2HC- and F_3C- .

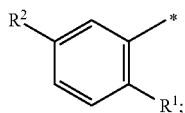
16. A compound according to claim 1, wherein R^7 is selected from the group R^{7b} consisting of H, phenyl, heteroaryl, cycloalkyl and heterocyclyl wherein the above mentioned phenyl, heteroaryl, cycloalkyl and heterocyclyl-groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, and C_{1-3} -alkyl-O— optionally substituted with 1 to 3 halogen atoms.

17. A compound according to claim 1, wherein R^7 is selected from the group R^{7c} consisting of H and phenyl, wherein the above mentioned phenyl group may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen and C_{1-3} -alkyl-O— optionally substituted with 1 to 3 halogen atoms. 25

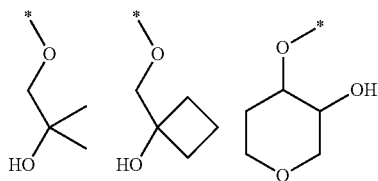
18. A compound according to claim 1, wherein R^8 is selected from the group R^{8b} consisting of C_{3-6} -cycloalkyl, heterocyclyl and heterocyclyl- C_{1-3} -alkyl-, wherein the above mentioned C_{3-6} -cycloalkyl, heterocyclyl and heterocyclyl- C_{1-3} -alkyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and C_{1-3} -alkyl- optionally substituted with 1 to 7 halogen atoms. 35

19. A compound according to claim 1, wherein R^8 is selected from the group R^{8c1} consisting of C_{3-6} -cycloalkyl and a saturated 4 to 6 membered monocyclic heterocycle containing one or two heteroatoms selected from N or O, wherein the above mentioned C_{3-6} -cycloalkyl and heterocyclyl-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and C_{1-3} -alkyl- optionally substituted with 1 to 7 halogen atoms. 45

20. A compound according to claim 1, wherein A is

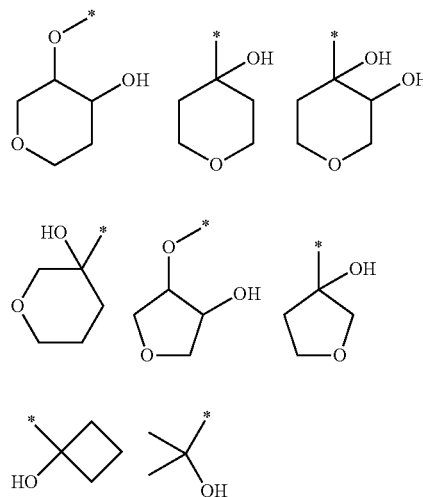


R^1 is selected from the group R^{1c1} consisting of H_3C- , fluorine and chlorine;
 R^2 is selected from the group R^{2f1} consisting of



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R^3 is selected from the group R^{3c} consisting of

H, H_3C- and cyclopropyl—,

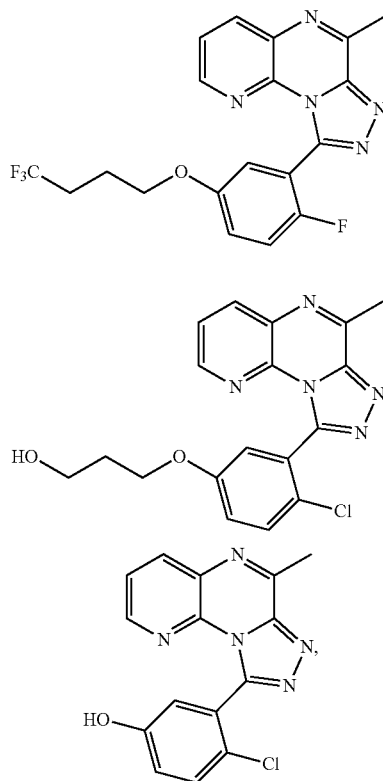
wherein the above mentioned H_3C- and cyclopropyl-groups may optionally be substituted with 1 to 3 fluorine atoms;

R^4 is H;

R^5 is H;

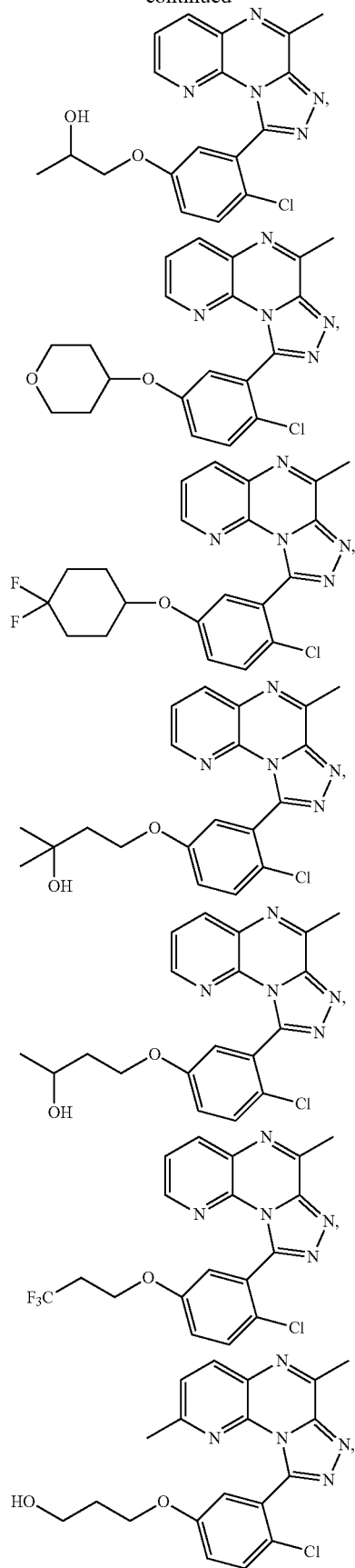
R^6 is H_3C- .

21. A compound according to claim 1, selected from the group consisting of:

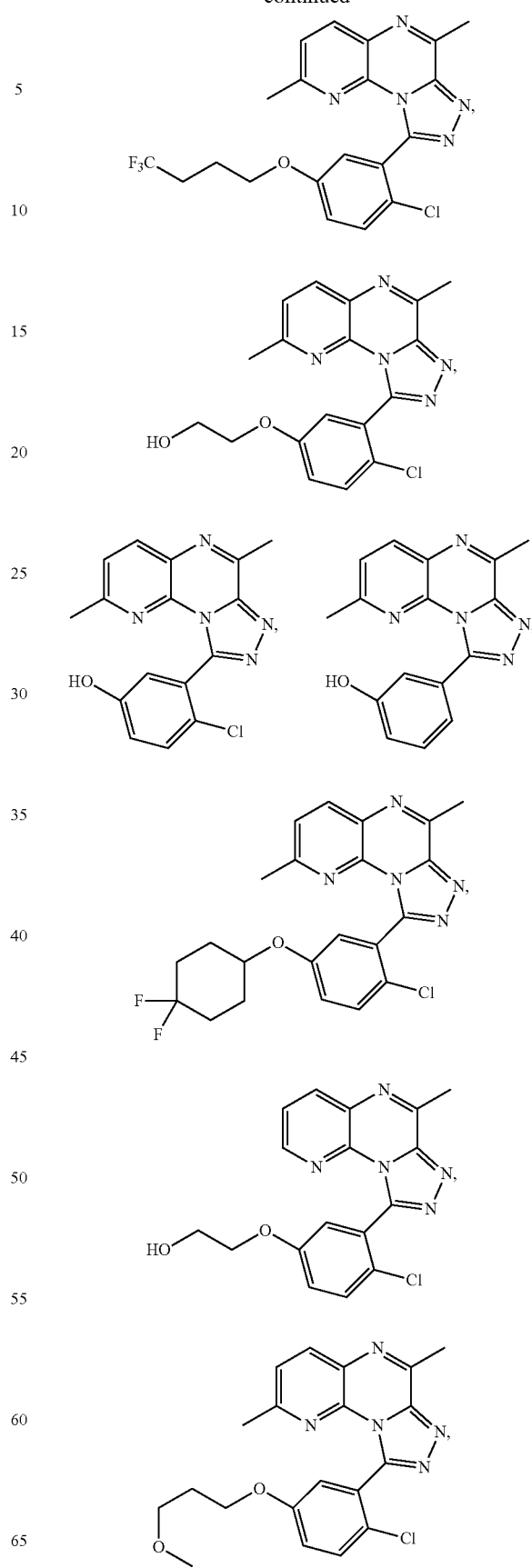


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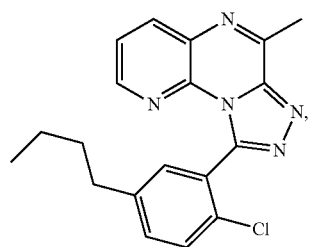
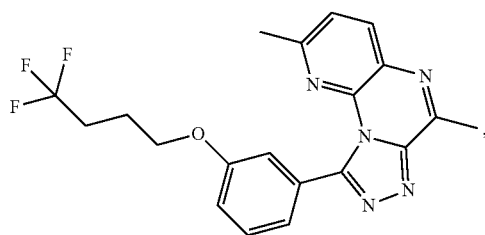
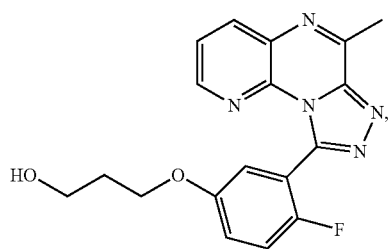
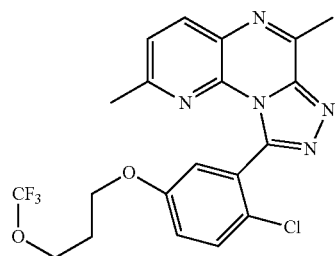
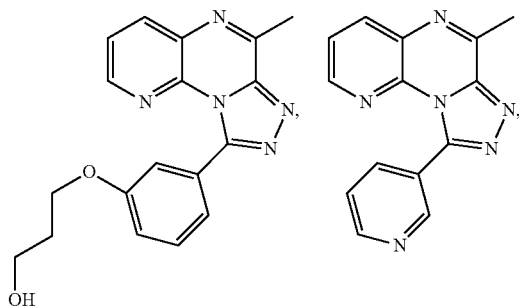
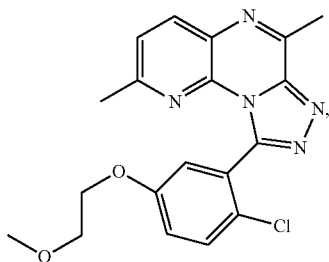
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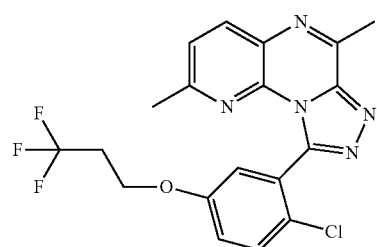
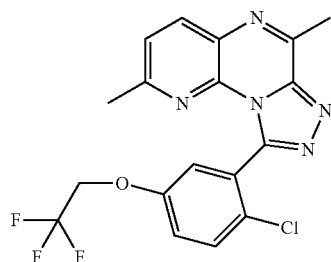
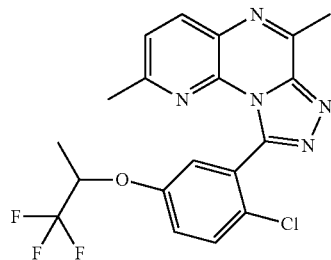
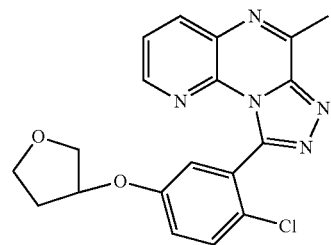
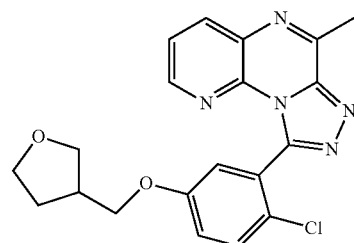
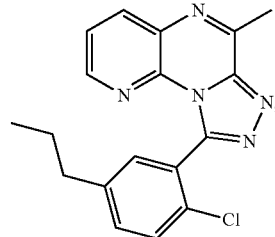


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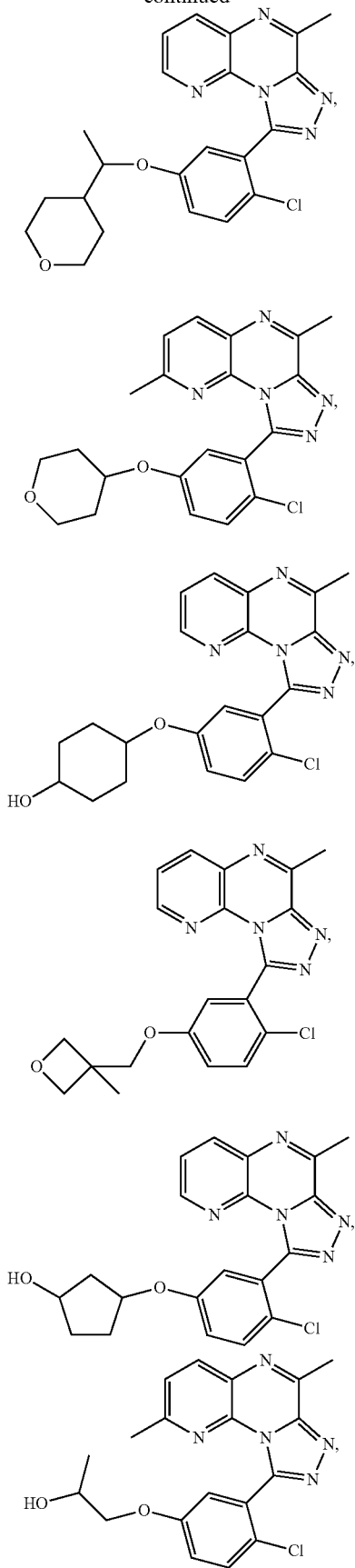
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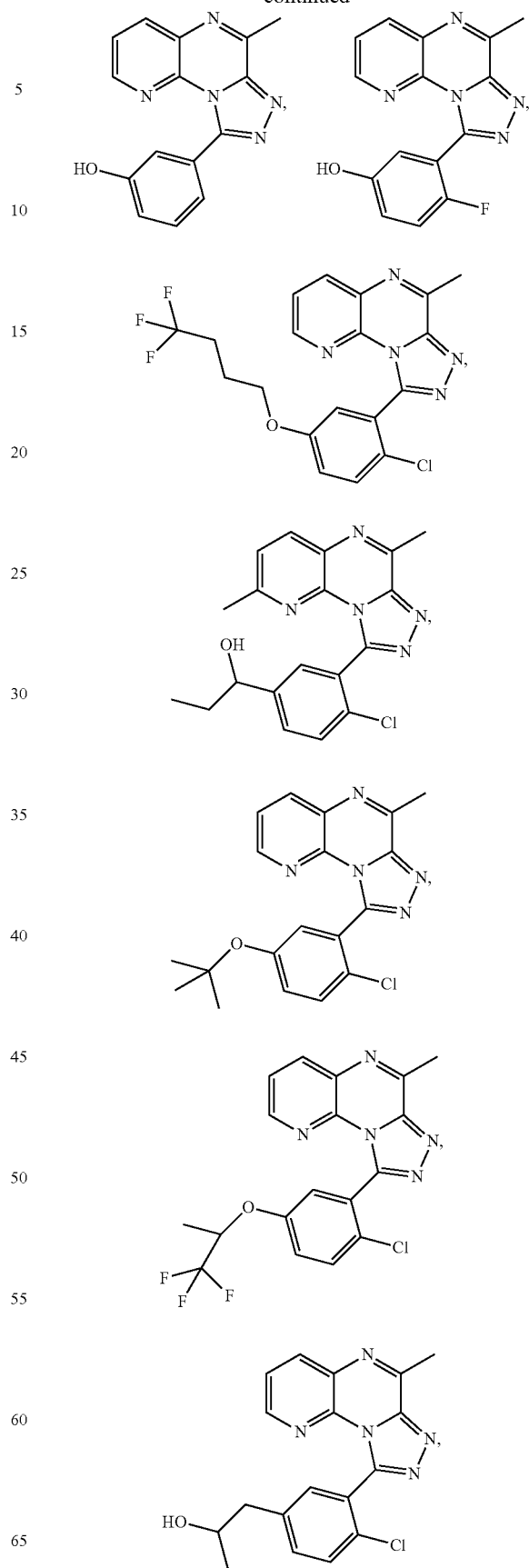


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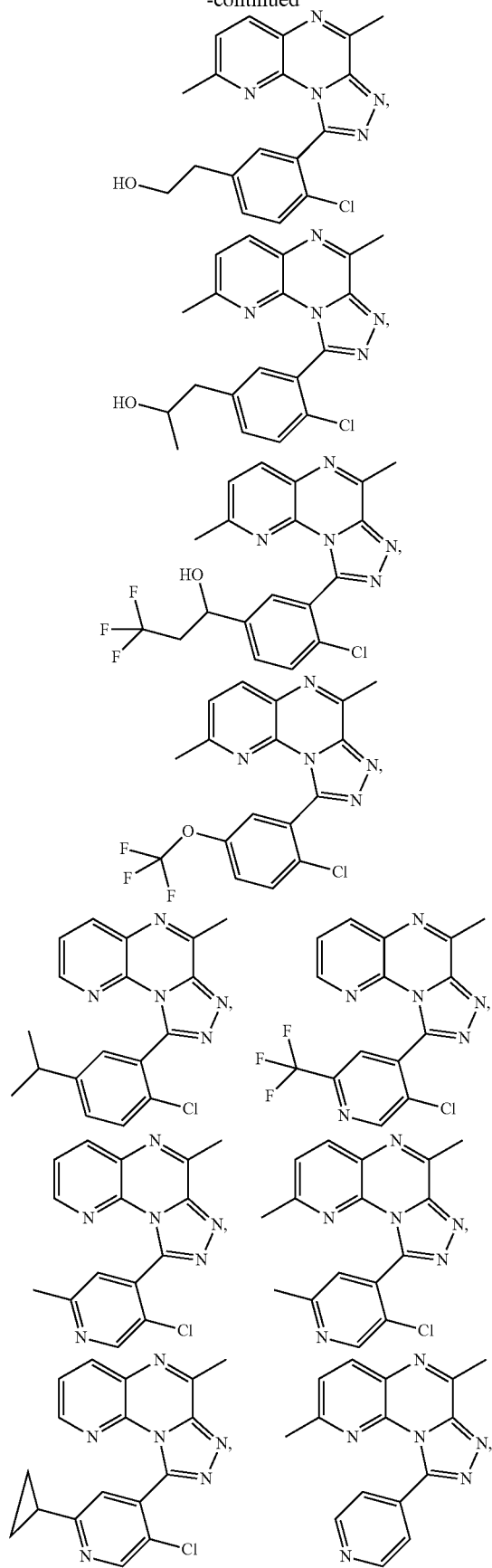
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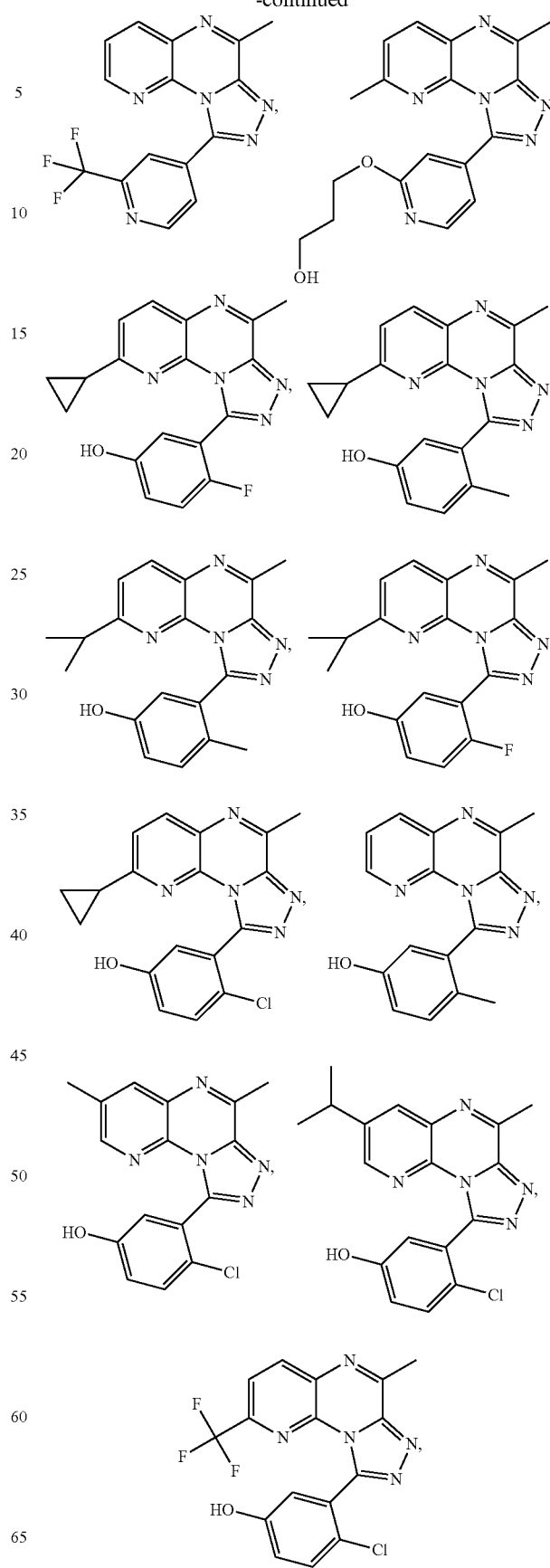


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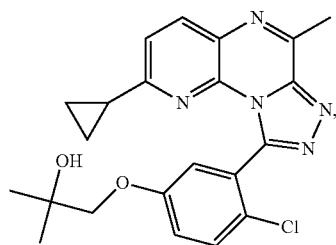
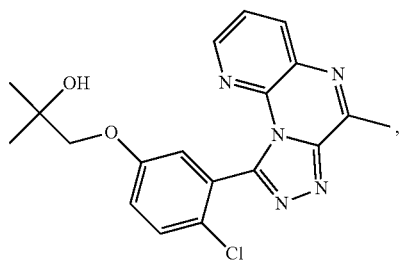
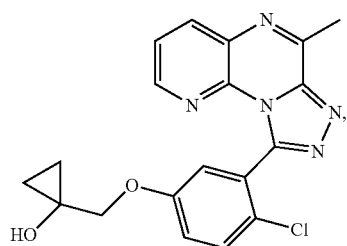
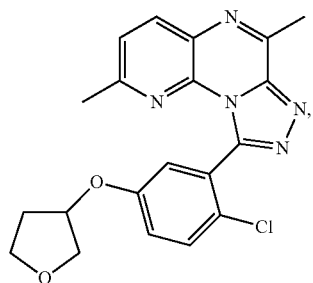
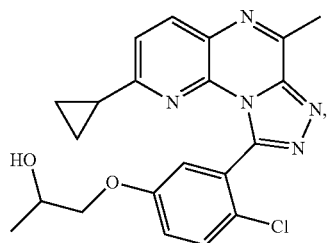
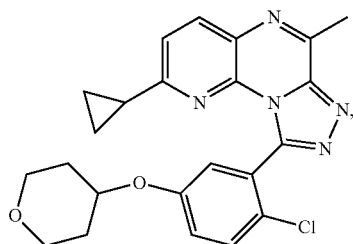
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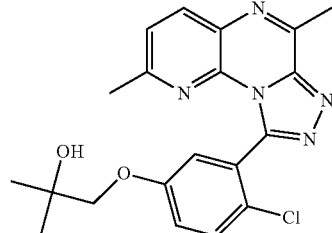
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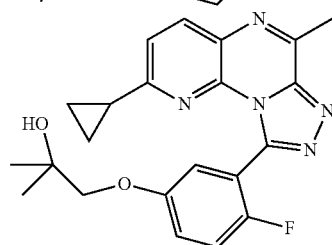
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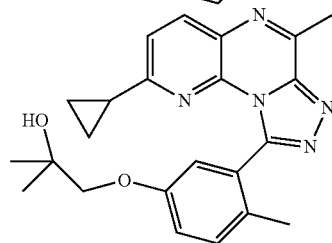
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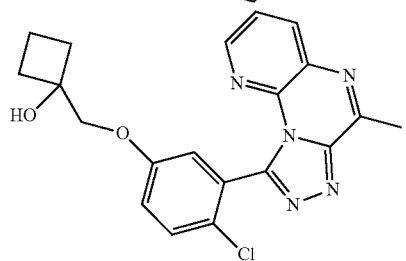
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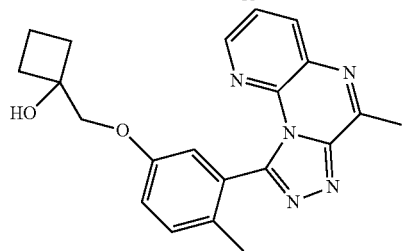
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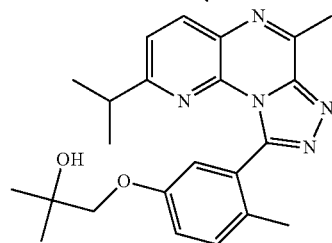
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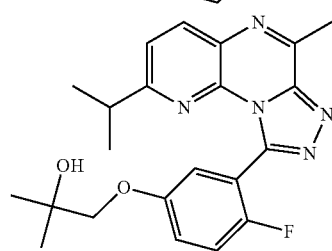
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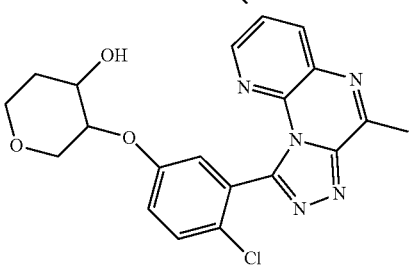
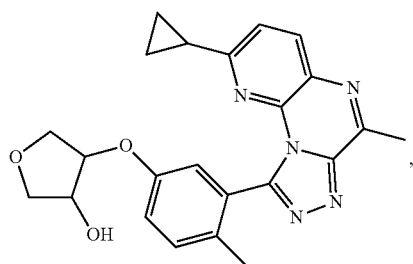
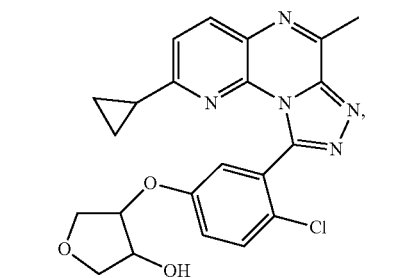
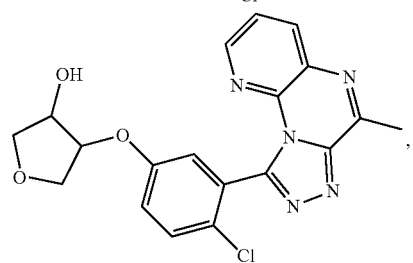
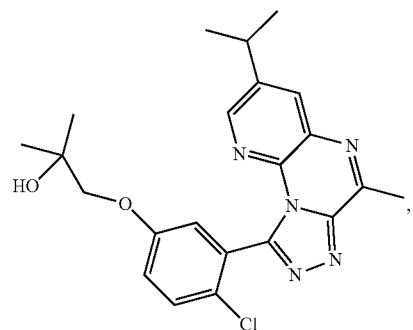
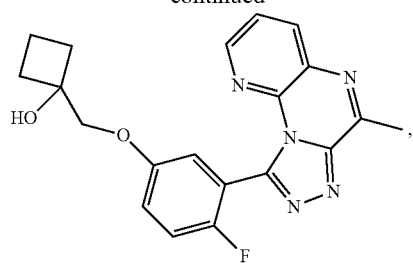
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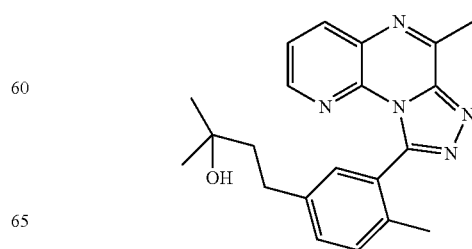
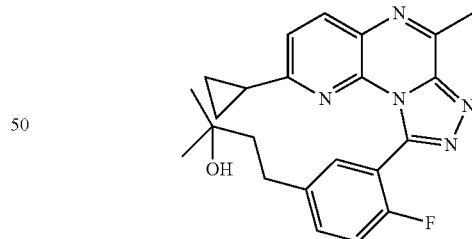
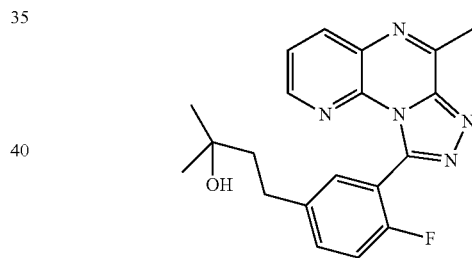
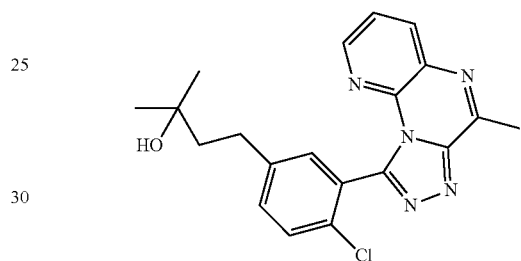
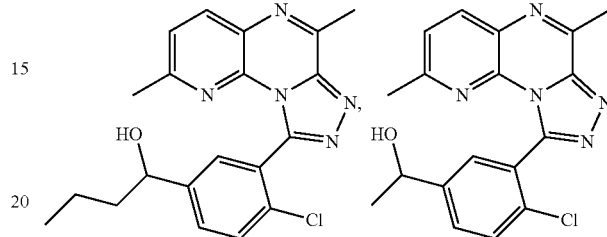
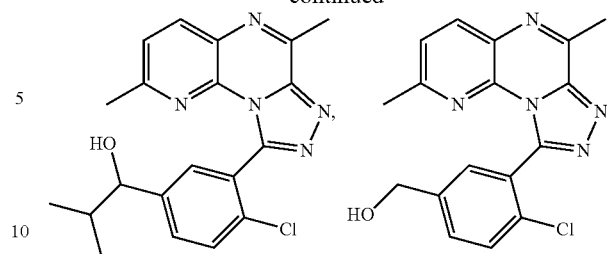


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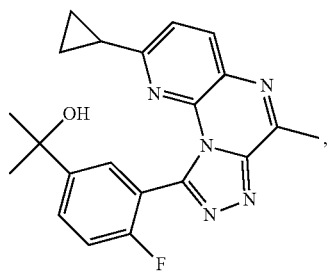
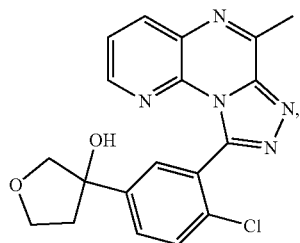
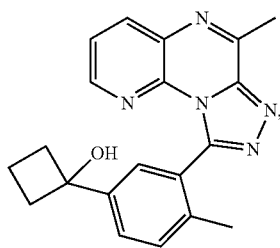
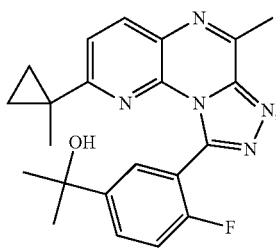
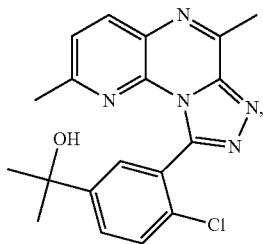
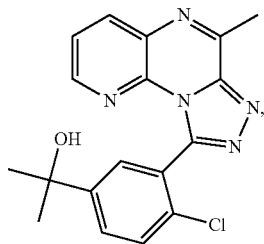
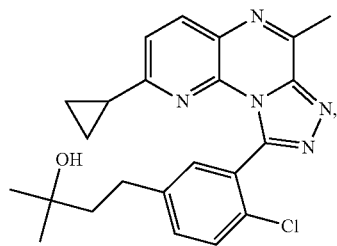
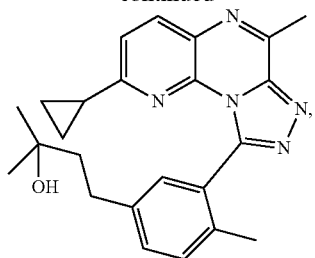
**206**

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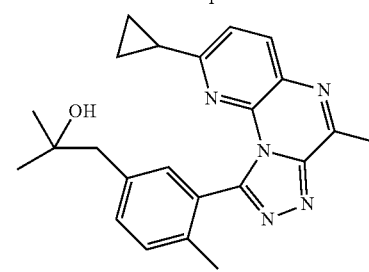
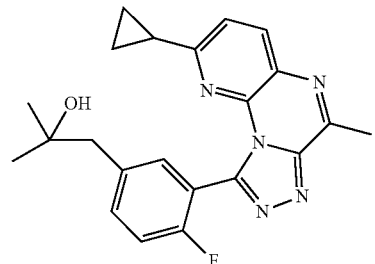
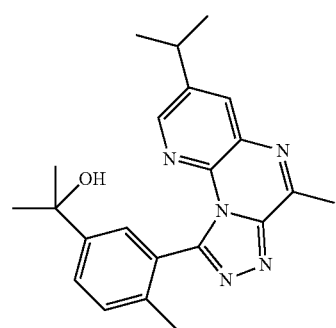
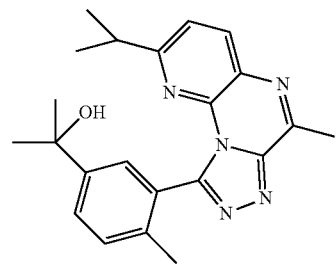
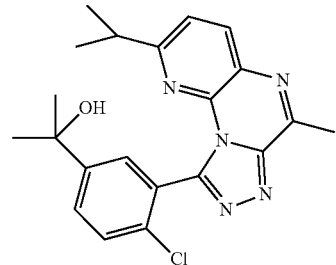
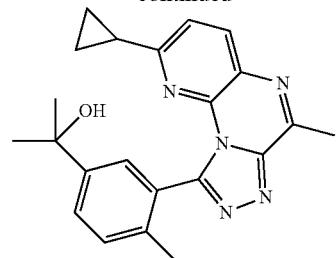


207

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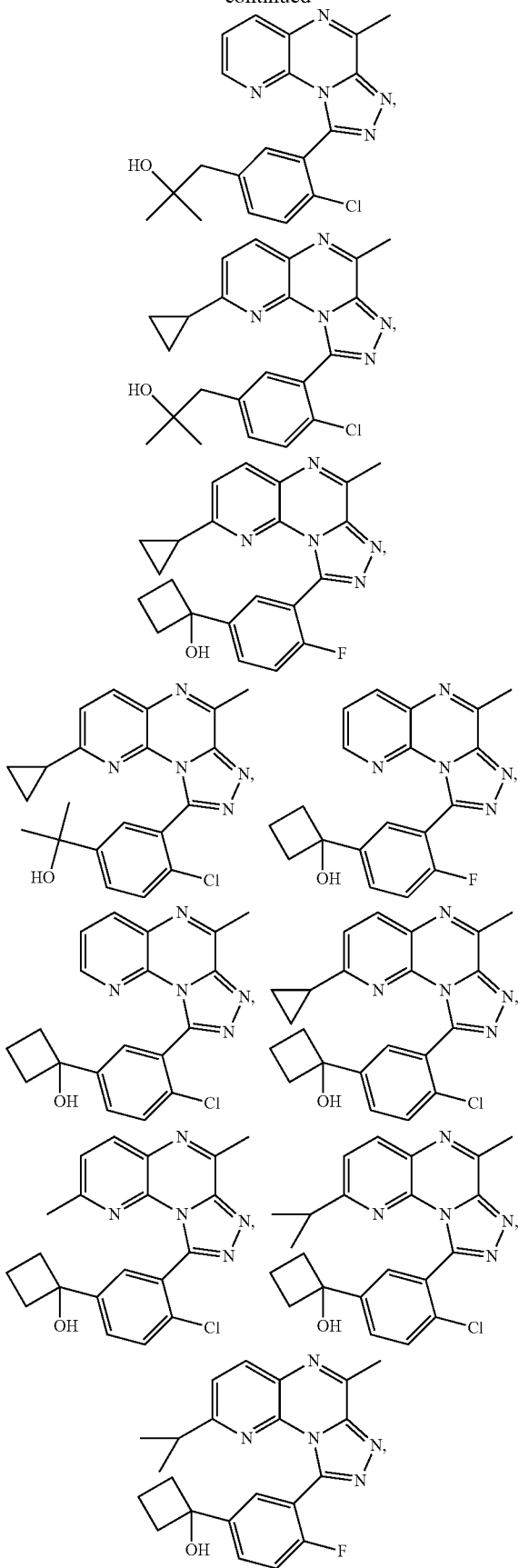
**208**

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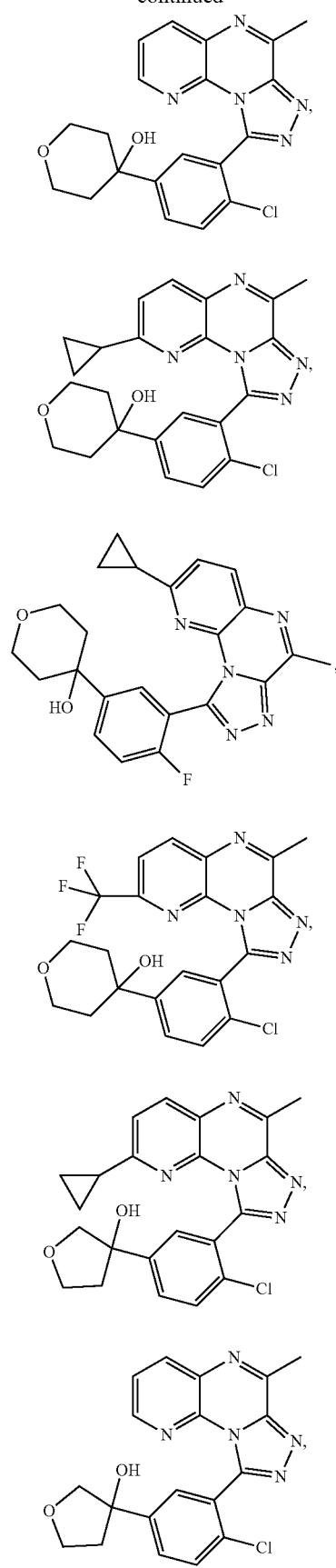


209

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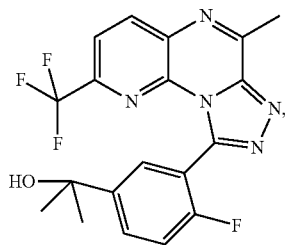
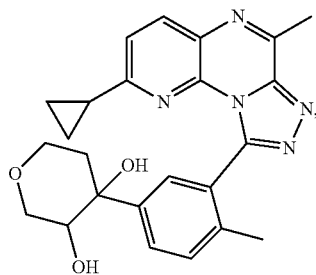
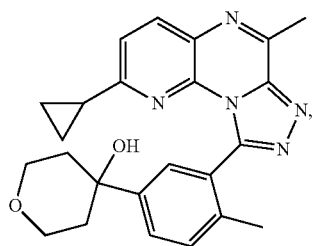
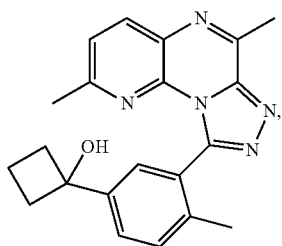
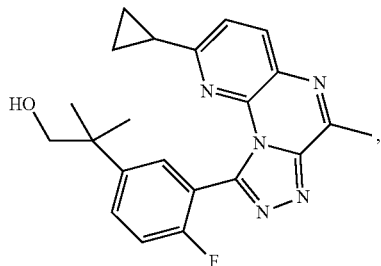
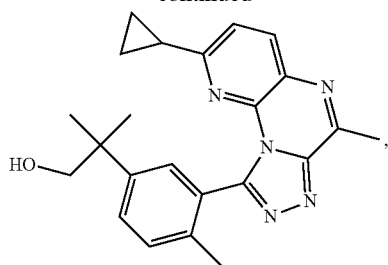
**210**

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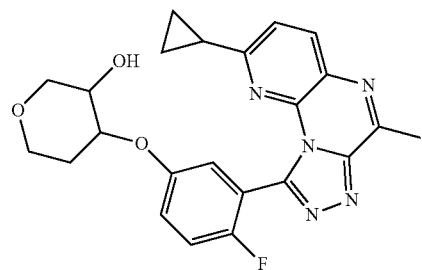
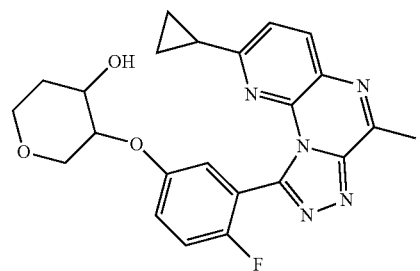
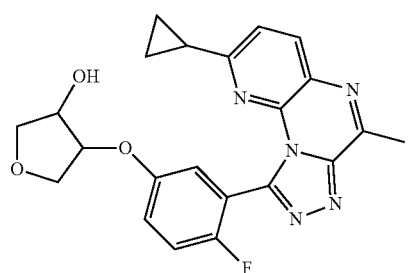
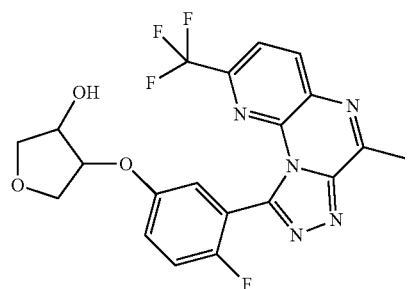
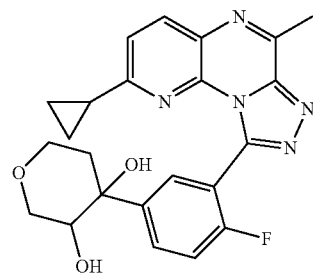
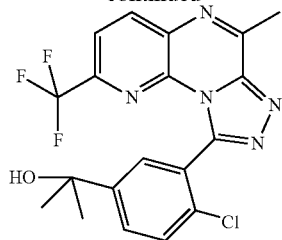


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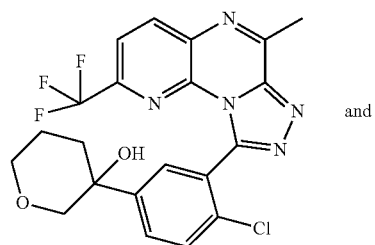
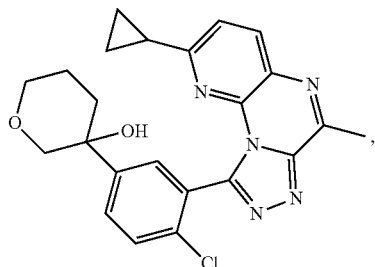
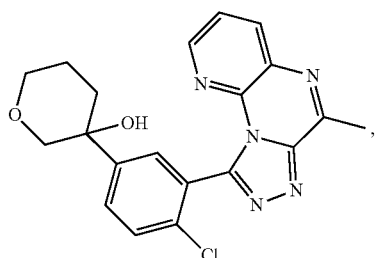
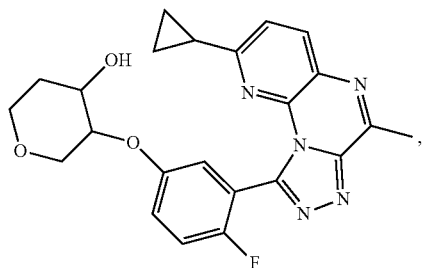
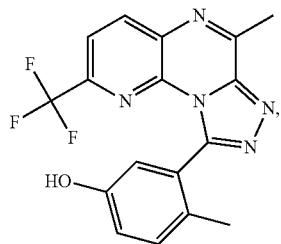
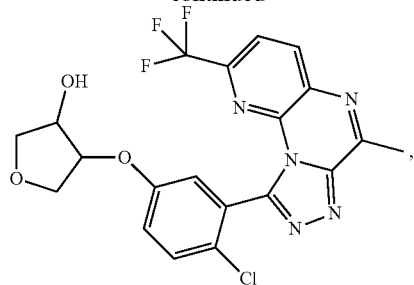
**212**

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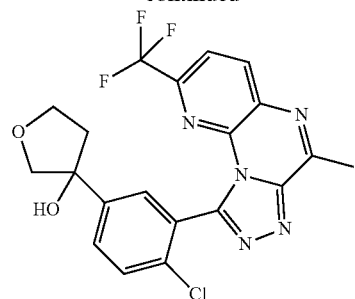
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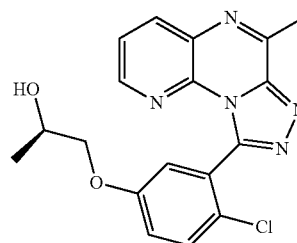
and

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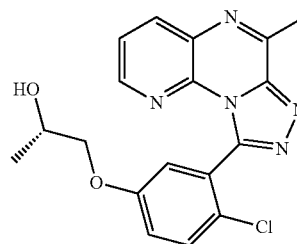
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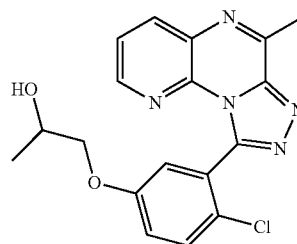
or a tautomer or pharmaceutically acceptable salt thereof.

22. The compound, according to claim 1, of the formula

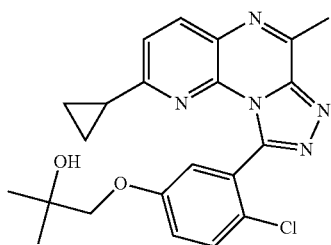
or a tautomer or pharmaceutically acceptable salt thereof.

23. The compound, according to claim 1, of the formula

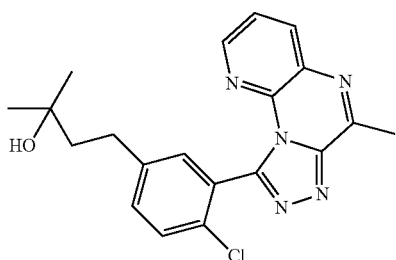
or a tautomer or pharmaceutically acceptable salt thereof.

24. The compound, according to claim 1, of the formula

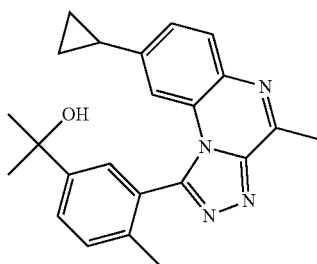
or a tautomer or pharmaceutically acceptable salt thereof.

215**25.** The compound, according to claim 1, of the formula

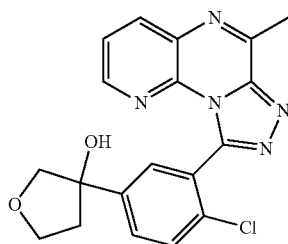
or a tautomer or pharmaceutically acceptable salt thereof.

26. The compound, according to claim 1, of the formula

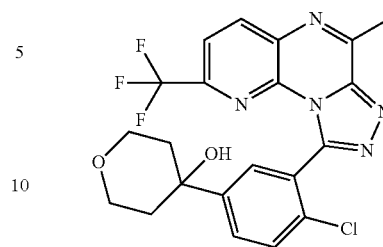
or a tautomer or pharmaceutically acceptable salt thereof.

27. The compound, according to claim 1, of the formula

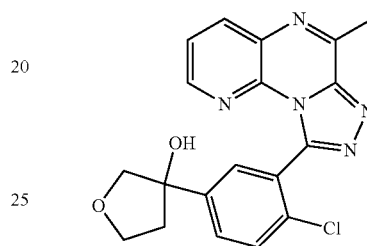
or a tautomer or pharmaceutically acceptable salt thereof.

28. The compound, according to claim 1, of the formula

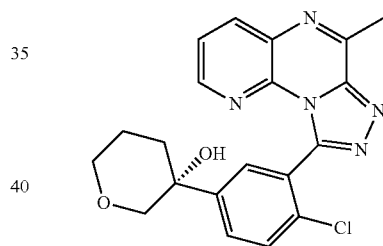
or a tautomer or pharmaceutically acceptable salt thereof.

216**29.** The compound, according to claim 1, of the formula

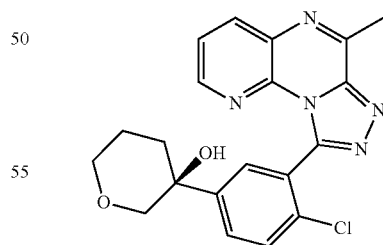
or a tautomer or pharmaceutically acceptable salt thereof.

30. The compound, according to claim 1, of the formula

or a tautomer or pharmaceutically acceptable salt thereof.

31. The enantiomer of the compound according to claim 30, of the formula

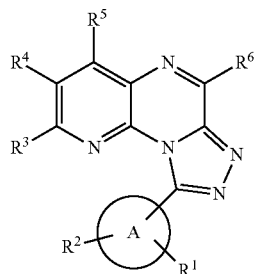
or a tautomer or pharmaceutically acceptable salt thereof.

32. The enantiomer of the compound according to claim 30, of the formula

or a tautomer or pharmaceutically acceptable salt thereof.

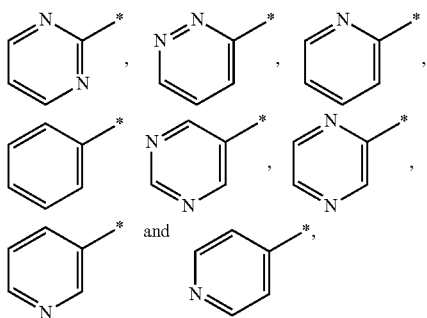
33. A pharmaceutical composition containing a compound according to claim 1 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.**34.** A method for inhibiting phosphodiesterase 2 activity and/or phosphodiesterase 10 activity in a host, which method comprises administering to said host an inhibitory amount of a compound of formula I

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wherein

A is selected from the group A^a consisting of



wherein the above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl- and pyrazinyl- groups are substituted with R¹ and R²;

R¹ is selected from the group R^{1a} consisting of

H, halogen, NC—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— wherein n is 0, 1, 2, 3 or 4,

wherein the above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl and R⁸—(CH₂)_n—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO— and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms;

R² is selected from the group R^{2a1} consisting of

HO—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— wherein n is 0, 1, 2, 3 or 4, and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— wherein m is 0, 1 or 2 and o is 0, 1 or 2

wherein the above mentioned C₁₋₆-alkyl- and C₁₋₆-alkyl-O— groups are substituted with 1 to 5 substituents independently selected from the group consisting of HO— and C₁₋₃-alkyl-O— optionally substituted with 1 to 7 fluorine atoms,

and

wherein the above mentioned C₁₋₆-alkyl- and C₁₋₆-alkyl-O— groups may optionally be substituted with 1 to 5 substituents independently selected

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from the group consisting of halogen and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms,

and

wherein the above mentioned C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸—(CH₂)_n—O— and R⁸—(CH₂)_m—(CH)(CH₃)—(CH₂)_o—O— groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO—, C₁₋₃-alkyl-O— optionally substituted with 1 to 7 fluorine atoms, and C₁₋₃-alkyl- optionally substituted with 1 to 7 fluorine atoms;

R³ is selected from the group R^{3a} consisting of

H, halogen, NC—, C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-, wherein the above mentioned C₁₋₄-alkyl- and C₃₋₆-cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC—, HO—, C₁₋₃-alkyl- and C₁₋₃-alkyl-O—;

R⁴ and R⁵ are selected independently of each other from the group R^{4a}/R^{5a} consisting of

H, halogen, NC—, HO—, C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O—,

wherein the above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O—, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl-, C₃₋₈-cycloalkyl-O—, heterocyclyl-O—, heterocyclyl, heteroaryl, R⁷—CH₂—O— and R⁷—(CH₂)₂—O— groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₂-alkyl- optionally substituted with 1 to 5 halogen atoms, and C₁₋₂-alkyl-O— optionally substituted with 1 to 5 halogen atoms;

R⁶ is selected from the group R^{6a} consisting of H, NC—, C₁₋₆-alkyl-, C₃₋₈-cycloalkyl-, C₃₋₈-cycloalkyl-C₁₋₃-alkyl- and C₃₋₈-cycloalkyl-O—

wherein the above mentioned C₁₋₆-alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of

H, carbocyclyl, heterocyclyl and heteroaryl, wherein the above mentioned carbocyclyl, heterocyclyl and heteroaryl- groups may optionally be substituted with 1 to 4 substituents independently selected from the group consisting of HO—, C₁₋₄-alkyl- optionally substituted with 1 to 3 halogen atoms, C₁₋₄-alkyl-O— optionally substituted with 1 to 3 halogen atoms and halogen; and

R⁸ is selected from the group R^{8a} consisting of C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl, wherein the above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of HO—, fluorine and C₁₋₃-alkyl- optionally substituted with 1 to 7 halogen atoms;

or a tautomer or pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,085,584 B2
APPLICATION NO. : 13/951531
DATED : July 21, 2015
INVENTOR(S) : Riccardo Giovannini et al.

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

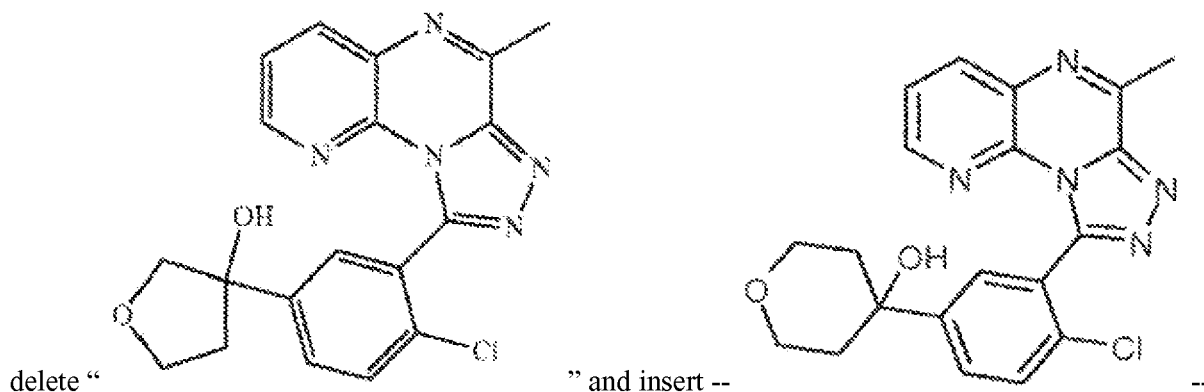
In the claims

In Claim 7, Column 191, line 41: "C₃₋₆-cycloalkyk" should read --C₃₋₆-cycloalkyl--

In Claim 8, Column 192, line 3: "C₃₋₆-cycloalkyk" should read --C₃₋₆-cycloalkyl--

In Claim 18, Column 193, line 30: "C₃₋₆-cycloalkyk" should read --C₃₋₆-cycloalkyl--

In Claim 28, Column 215, lines 53-66:



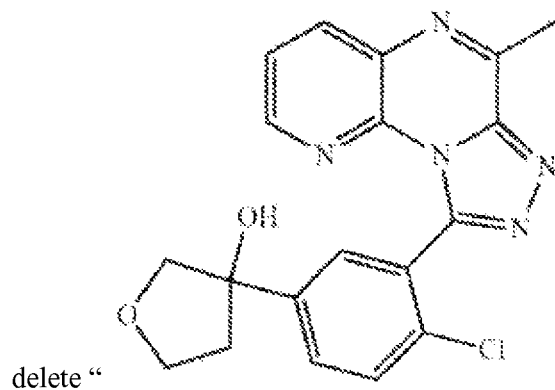
Signed and Sealed this
First Day of November, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

In the claims

In Claim 30, Column 216, lines 17-28:



” and insert --

